FACILITY AUTOMATION MANAGEMENT ENGINEERING SYSTEMS
33 Hoffman Avenue Lake Hiawatha, NJ 07034-1922

Friday, 30 April 2004

Documents Management Branch [**HFA-305**]
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 03D-0394

FORMAL COMMENTS ON:

"Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment [*G:\5831dft.doc 10/27/03*]."

Pursuant to a "request for comment" in ***FEDERAL REGISTER*, Vol. 68**, **No. 216**, pp 63109 – 63110.

BACKGROUND

A review of the Product Quality Research Institute (PQRI) 'recommendation' on which this guidance is based was submitted, on 25 September 2003, to CDER's Ombudsman, Warren Rumble, (via e-mail: **ombudsman@cder.fda.gov**) and, on 30 September 2003, to Dr. Ajaz Hussain, Deputy Director, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services (via e-mail: **hussaina@cder.fda.gov**).

On 15 November 2003, **FAME Systems** provided comments to this docket based on that review and an in-depth reading of the FDA's "**Draft Guidance for Industry on Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment** [*G:\5831dft.doc 10/27/03*]."

That review added elements that connect various issues in the Draft provided by the Agency to current good manufacturing practice (CGMP), in general, and the drug CGMP and other regulations with which this guidance is required to be congruent.

On 21 January 2004, **FAME Systems** provided a revised Draft Guidance, "**Guidance for Industry — Powder Blends And Dosage Units — In-Process Blend And Dosage Unit Inspection (Sampling And Evaluation) For Content Uniformity**" *after further review of the FDA's Draft and after in-depth discussions with Jon E. Clark.*

FAME Systems provided this revised guidance document to the Agency because the Draft provided by the Agency was clearly at odds with the fundamentals of CGMP, the clear strictures of **21 CFR Part 210** and **21 CFR Part 211**, and many aspects of sound inspection science.

To complete the comment process, **FAME Systems**:

- Has reviewed the formal comments, other than those submitted by **FAME Systems**, available electronically in Public Docket 2003D-0493 as of 1 April 2004 by those who commented against the fundamentals of CGMP, the clear strictures of **21 CFR Part 210** and **21 CFR Part 211**, and the basic precepts of sound inspection science.

- Is submitting the following scientific and CGMP-conformance assessment of those formal comments.
- Is planning to submit a follow on review of those comments published between 1 April 2004 and 30 April 2004 should such become available in the e-Docket for Public Docket 2003D-0493.

To clearly separate **FAME Systems'** review statements from the formal comments of those who submitted such, the review comments are in an **Arial** or ***italicized Arial*** font and the original commenters' submissions are in a **Times New Roman** or the other fonts used by the commenters.

In general, the available formal comments will be reviewed by the Agency's posting category, "C" or "EMC," and then in the order they were posted to the docket.

For simplicity, each commenting firm or group will be addressed in the singular even when the comments are clearly from multiple persons.

When either a binding regulation or a statute is quoted, the text is in a **Lydian** font.

When other recognized sources are quoted, a **Perpetua** font is used.

Should anyone who reads this review find that its guidance is at odds with sound inspection science or the applicable CGMP regulations, or that additional clarification is needed in a given area, then, in addition to providing the sound science or rationale that refutes the review text provided, or his or her clarifying comments to the public docket, he or she is asked to e-mail **drking@dr-king.com** a copy of that sound science, rationale, and/or commentary.

Respectfully,

Dr. King

C-01 Comments By Hikma Pharmaceuticals, Posted 18 December2003

Hikma begins by stating:

"Referring to the Draft Guidance for Industry on " **Powder Blends and Finished Dosage Units - Stratified In-Process Dosage Unit Sampling and Assessment**" **[Docket No. 2003D-0493]** . Published on the 27th of October 2003 .

And considering that this guidance document is being distributed for comment purposes, we would like to send you some comments and suggestions regarding this draft.

…

Hopefully our comments will be taken positively."

Hikma's reviewed comments are as follows:

"**1. Section 1V.B: CORRELATION OF IN-PROCESS STRATIFIED SAMPLING WITH POWDER MIX AND FINISHED PRODUCT,** ***correlation of powder mix uniformity with stratified in-process dosage unit data:***

1.1. The compression or filling processes in this guidance are divided into a minimum of 20 sampling locations with at least 7 samples taken from each location. This is applied for process development batches and validation batches. The point that I would like to mention here is that during a validation batch with a batch size of for example l,000,000 units and machine speed of 60,000 units per hour, the compression or filling cycle could take up to 1000 minutes to be completed, this may give sufficient time to take samples as per this guidance, i.e. taking samples every 50 minutes.

1.2. While in the exhibit batches, usually the batch size is one tenth of the validation batch size, this sampling intervals may not be convenient.

1.3. Based on the above example the batch size of the exhibit batch is 100,000 units and the compression or filling cycle will be completed in about 100 minutes, i.e. the samples will be taken every 5 minutes which is not convenient and appropriate.

1.4. **It is mentioned in the same section that this 20 locations strategy with 7 samples each should be used for process development batches, validation batches and routine manufacturing batches for approved products.**

1.5. While in section V1.D **"VERIFICATION OF MANUFACTURING CRITERIA,** ***sample locations for routine manufacturing*****"** the guidance recommended that during routine manufacturing at least 10 sampling locations during capsule filling or tablet compression should be identified to represent the entire routine manufacturing batch.

1.6. I feel that this point is not clear and that the number of sampling locations should be the same in both sections for routine manufacturing batches

1.7. Our suggestion for that point is as follows: Provided that the manufacturing process is fully and successfully validated, and knowing that validation assures the product quality and calls for reduced sampling during routine manufacturing, we recommend to follow the sampling strategy described in section VI.D rather than that mentioned in Section IV.B for routine manufacturing batches of approved products."

While this reviewer agrees with this commenter that the sampling plans proposed for the formed units are problematic, this reviewer has different concerns.

First, the Agency's Draft guidance fails to require the samples sampled and tested to be ***representative*** of the batch as required by **21 CFR 211.160(b)(2)**.

When the draft guidance suggests that the emphasis in the blend should be to sample from where the blend is thought to be more variable, the resulting samples cannot *validly* be represented to be ***representative*** of the blend.

When *dynamic* (time point) sampling is performed to collect the formed dosage unit samples, to be ***representative***, **minimally:**

1. The number of units taken at each time point **must** be some integer multiple of the number of dosage-unit forming stations in the equipment used.
2. The number of time points of sampling **must: a)** span the batch and **b)** be sufficiently frequent to reveal and track any time-related non-uniformity in the dosage units formed.

Second, the Agency's Draft guidance does not explicitly address the CGMP requirement for the ***testing of representative*** numbers of units that span the production step from the ***samples*** sampled.

Third, the Agency's Draft guidance fails to address the CGMP requirement to "monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product" in the manner required by **21 CFR 211.110** where, *for the tablet and capsule drug products this Draft emphasizes*, "Such control procedures shall include, but are not limited to, the following, where appropriate: (1) Tablet or capsule weight variation; (2) Disintegration time; (3) Adequacy of mixing to assure uniformity and homogeneity; (4) Dissolution time and rate; …" where, *in addition to addressing active uniformity*, weight, disintegration, dissolution time and rate, and other critical variable factors should be appropriately addressed for the formed dosage units and/or the finished dosage units.

Moreover, for the final blend, more than the uniformity of the active must be monitored (minimally, **a)** the uniformity of the lubricant [because it impacts "equipment function"] **and b**) the ingredient or ingredients added to control the release of the active or actives [because such control active availability]).

Further, this reviewer agrees with the commenter that the Agency's Draft guidance on sampling time points should be revised to be more flexible and, to the extent possible, should not be overly prescriptive.

However, this reviewer would propose that the guidance be cast in terms of:

- A "start" sampling,
- "n" approximately equally spaced time-point samplings, and
- An "end" sampling with
- Provision for "substitute" or "additional" samples after any interruption in the forming of the dosage units and, if expected, any other significant event in the forming process.

This pattern should include the restriction that the total number of sampling points selected should be proven to be sufficient to monitor the non-uniformities in the formed dosage units that are introduced by variations in either: **a)** the blend used **or b)** the dosage-forming process.

Beyond the preceding restrictions, this reviewer would recommend that, *in general*, the "n" should be an integer value greater than four (4).

"**2. Section VI: VERIFICATION OF MANUFACTURING CRITERIA - B. criteria to meet the readily pass classification, and C. criteria to meet the marginally pass classification.**

2.1. The third criteria in both sections is: "*all individual results are within the range of 75.0% to 125.0 % of target strength "*, in fact our comment on this point is that in general this range seems to be wider than enough and a more narrow range will be appropriate

2.2. Another point considering this criteria is that when it is correlated with the first criteria in the readily pass classification which is: 'for all individual results for each batch ($n \geq 60$) the RSD ≤ 4.0 %', These two criteria are contradicted, I mean that assuming that our 60 samples reading are all the same for example 100 % and we only have one point equals 75 % and another point equals 125%, still the RSD value will be more than 4.0% (equals 4.6%), in spite of meeting the second and third criteria. See example in attachment # (1) .

2.3. On the other hand the RSD value criteria can be better achieved (3.68) if the individual results range was more narrow than the one mentioned in the draft, for example to be from 80% to 120%. See the example in attachment # (2) .

2.4. Based on the above discussion and examples we comment that the RSD value for readily pass criteria can be increased to < 5.0 %. And the range of individual results for both readily pass classification and marginally pass classification can be tightened to 80.0% to 120 % range (instead of 75% to 125%)."

This reviewer cannot agree with the commenter's remarks or with the rationales that were used.

The CGMP regulations require all specifications to be ***scientifically sound*** and ***appropriate***.

Neither the specifications proposed in the Agency's Draft nor those proposed by this commenter are **scientifically sound** and **appropriate** for the testing of a small number of units from a population that is, at production scale, four or more orders of magnitude larger.

As has been previously stated, the recognized consensus standards, **ANSI/ASQC Z1.9**-1993, "**SAMPLING PROCEDURES AND TABLES FOR INSPECTION BY VARIABLES FOR PERCENT NONCONFORMING**," American Society for Quality, (ASQ), 611 East Wisconsin Avenue, P.O. Box 3005, Milwaukee WI 53201-3005, USA, Tel.: 1-800-248-1946 Ext 7244 or 1-414-272-8575 (or its ISO equivalent, ISO 3951:1989), set forth (*at the 95 % confidence level*) sampling plans that CLEARLY establish the minimum number of *tested* ***representative*** *samples* whose valid results can be used to *scientifically* predict whether or not the untested majority of the batch is, *or is NOT*, acceptable (as a manufacturer **must** do to meet the CLEAR requirement ***minimums*** established in **21 CFR 211.165(d)** for batch acceptance for release).

In general, because all of the critical variable properties (chemical and physical) of the components used in the formulation of the final blend from which the dosage units are formed are not rigorously controlled, the ***minimum*** sample sizes are those established for the appropriate "NORMAL," "PROCESS VARIABILITY UNKNOWN" sampling plans in aforesaid consensus standards.

Further, the referenced consensus standards initially require (*during the initial performance qualification studies [also known as the initial Validation]*) that not less than (NLT) 200 ***batch-representative*** units should be tested (whenever the batch size exceeds 150,000 units) for the primary variable factor examined (*in the Agency's Draft guidance that factor is the active content of the dosage units*).

Thus, initially, a manufacturer of full-scale batches larger than 150,000 units should test not less than 200 ***batch-representative*** units for their active content, **unless** the firm has proven that, *under worst-case conditions (maximum permitted variability in all the critical variable characteristics [chemical and physical] and worst-case processing control variation for all of the process steps leading up to the formed dosage units)*:

- Final blend's uniformity vis-à-vis active content is acceptably uniform **and**
- Worst-case dosage forming controls produce acceptably uniform dosage units.

[**Note**: In general, most firms lack the requisite controls on one or more of the critical physical characteristics (of the components used to manufacture the various blends and the final product) required to satisfy the exception condition outlined.]

*Having developed processes that produce **UNIFORM** final blends with an RSD of 1.5 %, or less (for multiple measurement on tens of samples from each batch)*, this reviewer knows that a distribution spanning approach that uses the general "rules of thumb" properties of distributions should be used to set the scientifically sound acceptance range for the uniformity of a batch of drug product with respect to each variable factor that **must** be evaluated.

In general, for "Content Uniformity," since the relative range "85 % to 115 %" is the general upper limit for the range for any post-release expected value (the **USP**'s "any article in commerce") and "75 % to 125 %" is the general limit relative range for any acceptable value for any post-release value, one can use see that the expected range spans 60 % of the "any unit" range.

Presuming that today's CGMP goal should be to EXPECT to produce units that have "6 sigma" quality, the upper limit on the expected RSD should be [(115 – 85) / 12 sigma] divided by approximately (1 + the variability fraction uncertainty introduced by the measuring of a small number of units [or ~ {1 + "f"}) or [(30) / 12 sigma] / ~ {1 + P}.

Presuming:

- **A 95 % confidence level is needed** (the least justifiable confidence level for batches larger than about 10,000 units) **and**
- **The valid results from a tested sample of *any* size drawn from a *representative sampling of* that *batch* can be *representative* of the *batch*** (*a questionable assumption, at best, for sample sizes under 60 units*),

the manufacturer can use the standard variability nomograph published in any of a number of statistics texts that address the uncertainty in the population variability based on the observed variability in the samples tested to determine the upper limit on RSD, the following approximate RSD limits apply for a $\text{sigma}_{\text{batch}}$ of 2.5:

Number of "Representative" Units Tested	Approximate "f"	Effective Upper Limit "RSD" for Acceptance
10	0.45	1.72
30	0.25	2.00
60	0.18	2.12
200	0.083	2.31
750	0.05	2.38

Based on the values found, the preceding are **UPPER** 95-%-CONFIDENCE-LEVEL **LIMIT** values for the observed RSD (for the number of batch-representative samples tested) that is required to ensure that the batch's RSD is less than the established requirement of ***not more than*** 2.5 % for the RSD for the ***batch*.**

That sample RSD limit value:

A. Decreases as the number of representative samples declines, and

B. Imposes a smaller value on the OBSERVED UPPER LIMIT of the Final Blend used to form the dosage units than the acceptable RSD value for the dosage units.

Since the $RSD_{Dosage\ Units}$ is the square root of the sum of: **a)** the variance in the content in the Final Blend, **b)** the variance in the weight of the dosage units, and **c)** the variance introduced by the dosage-forming process, attempts to set the test sample sizes from the ***representative*** *samples* sampled to small numbers (if such were justifiable) would require, *even if the true relative variance for the Final Blend were to be not more than 1*, the sum of the weight variance and the dosage-unit-forming (including any material storage and transfer components thereof) to be on the order of "2" or less – values that are less than those often observed in the typical dosage-unit-forming process steps.

Based on the preceding, this reviewer's understanding of the RSD realities vis-à-vis Final Blends and dosage-unit weight variation, and the proposed numbers of samples, this reviewer cannot support the proposed sample numbers because they are neither ***scientifically sound*** nor ***appropriate*** for the processes being discussed.

In general, this reviewer recommends that the Agency guidance should:

- Establish the validity of their specifications by appropriately applying the restrictions that sampling science suggests should be used to derive valid batch acceptance specifications and specification ranges that are appropriately inside of the binding post-release "any sample in commerce" requirements set by the **USP** (***where such exist,*** **the USP's expectation limits or ranges should be used as the basis for setting the permitted variability restrictions on the observations from the *testing* of "n" sample units from a *population-representative sample* of units for any critical variable property**).
- Use the recognized consensus standards alluded to previously as the ***minimum*** basis that manufacturers should use to appropriately justify the number of ***representative*** sample units that should be *tested* to ensure that the batch, *not just the samples tested*, is acceptable. [**Note:** *Though outside*

of this discussion, those who wish to classify rather than test samples should recognize that the applicable consensus standard is **ANSI Z1.4** or its appropriate **ISO** equivalent.]

Hopefully, the preceding reviewer's remarks have adequately addressed this commenter's comments.

C-02 Comments By GlaxoSmithKline, Posted 8 March 2004

GlaxoSmithKline begins by stating:

"Enclosed please find comments from GlaxoSmithKline, including general and specific comments, for the Draft Guidance for Industry on Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment. These comments are presented for consideration by the FDA. The general comments are presented first, with specific comments presented in order by section and line number in the draft guidance. An appendix with the statistical rationale to support our comments is also included."

GlaxoSmithKline's reviewed comments are as follows:

"**GENERAL COMMENTS**

The criteria for blend homogeneity have been carried forward and are applied to uncoated tablet cores. FDA's premise for tighter in-process controls for blend homogeneity was that there are additional processes between the blending stage and the compression stage that could lead to further segregation (transfer of blend into hopper of the rotary compression press, within the hopper and feed chute of the rotary compression press, etc.). However, there are no processing stages between tablet cores and coated tablets that can impinge on the homogeneity of the finished product (only coating), and therefore there should be no difference in the testing criteria of tablet cores and coated tablets, with respect to homogeneity."

> *While most of what the commenter states may be true*, the commenter's remarks do <u>not</u> address capsule products even though the draft guidance does.
>
> Moreover, *contrary to the position stated*, the coating process can affect the ***uniformity*** of critical variable factors, such as active availability and, in some cases (e.g., erosion and mass transfer, or the addition of active in the coating {as is done in some cases), active content.
>
> Thus, the commenter's remarks concerning that "there should be no difference in the testing criteria of tablet cores and coated tablets, with respect to homogeneity" is <u>not</u> generally supportable.

"The relative standard deviation (RSD) criteria for readily pass (not more than 4%, or NMT 4%) or marginally pass (NMT 6%) for the uncoated tablets are much more stringent than the existing USP counterparts: USP I (NMT 6 %) or USP II (NMT 7.8%)."

1. The criteria proposed in any CGMP-complaint draft guidance must be criteria for ***batch-representative samples***.
2. The post-release, in-commence, "***any article***" criteria in the **USP** are for any grab sample, a sample that is, *by definition*, <u>not</u> ***batch representative***.
3. *Because the <u>basis</u> for the two samples <u>is</u> <u>not</u> the <u>same</u>*, it is <u>not</u> *scientifically sound* to directly compare the two criteria. [**Note:** By analogy, those who do so are guilty of attempting to compare "Granny Smith" apples and "Valencia" oranges as if they were both varieties of apples.]

"There is a reasonably high chance (ca. 60%) of batches with high RSDs failing the new in-process stage 2 criteria, but passing the existing USP criteria."

The preceding statement is meaningless because the **USP** provides no RSD criteria for *batches* – the **USP**'s criteria apply only to any tested *article* – *the sample*.

Factually, batches passing the proposed criteria have a significant probability that some *article* or *articles* in the batch will not, *if tested*, pass one or more of the **USP**'s criteria.

The controlling **USP** criteria for ***any article*** are as follows:

1. The ***article*** for uniformity assessment is any 30 dosage units
2. ALL units in the ***article*** MUST have relative content values between 75 % and 125 % of their appropriate target value (usually 100 % of label claim).
3. ALL units in the article ARE EXPECTED to have relative content values between 85 % and 115 % of the target.
4. For tablets, ***NOT MORE THAN*** one unit (1) in any tested article can have a relative content value that is outside of the "85 % to 115%" range (for capsules the "outside of" limit is 1 or 2 capsules).
5. The RSD for ***any*** *subarticle* (10 units) in any article (30) MUST not exceed 6.0 %.
6. The RSD for ***any article*** MUST not exceed 7.8 %

"This guidance should provide criteria that are consistent with the USP criteria. (See statistical rationale for support for in Appendix 1.)"

While this reviewer agrees wholeheartedly with the commenter's statement, neither the draft guidance nor the commenter's remarks do "provide criteria that are consistent with the USP criteria."

*Considering that the **USP** criteria apply to **any article** and a **batch** consists of a random collection of thousands of **articles***, one needs to develop valid criteria for the results from the testing of a ***representative sample*** (*as that term is defined in **21 CFR 210.3(b)(21)***) from the ***batch*** that will ensure that each and every ***article*** in the batch will, *if tested*, probably meet ALL six (6) of the **USP**'s criteria at a confidence level of at least 95% – such criteria will then be consistent with the **USP** criteria.

Properly, the focus of the development of said **USP**-consistent criteria should be the transformation of the allowed frequency of values outside of the **USP**'s "85 % to 115 %" range in the ***article*** (1 in any 30) into the corresponding excursion frequency expectation for the testing of a valid: **a)** ***in-process batch-representative sample*** (as required by **21 CFR Part 211.160(b)(2)**) or **b)** ***drug-product batch-representative sample*** (as required by **21 CFR 211.160(b)(3)**).

Obviously, the upper limit for a ***batch*** should be less than 1 in ***any*** 30 (3.3 %) for "tablets" (or less than 2 in ***any*** 30 [6.67 %] for "capsules").

ESTABLISHING CGMP COMPLIANT SPECIFICATIONS

Considering tablets, direct translation of the **USP** "inner" (85 % to 115 %) and "outer" limits (75 % to 125 %) from the article to a uniform distribution (*required to satisfy **21 CFR 211.110***) implies that the acceptable population is a 50 % range and the expected population is a 30 % range.

Considering the preceding in terms of the ***uniform*** distribution that such units must be, one finds that 60 % (30/50) of the permissible range for units in a batch are expected to contain ***not less than*** about 96.7 % of the population for tablet products (or ***not less than*** about 93.3 % of the population for capsules).

Considering that the active content values for the dosage units in a batch are approximately normally distributed, one can use the preceding to describe the desired distribution in terms of "sigma," the true variability of the batch.

Two scenarios come to mind to address the requirements for the in-process uniformity of the formed dosage units and the drug product as set forth in the **21 CFR 211.110**.

The first is one that would have been "universally" appropriate at in the late 1970's and could still be appropriate for batches of tablet and capsule drug products that consist of not more than 10,000 dosage units.

The second scenario is one that matches ***current good manufacturing practice*** (where the goal is to manufacturer **all** units so that each has an active content that is within the **USP**'s EXPECTED relative range ("85 % to 115 %) in a manner that each unit is expected to have an active content that is within +/- 6 sigma of the drug product's CGMP target.

The second scenario becomes the one that firms should use whenever the nominal batch size for the drug product exceeds 1,000,000 dosage units.

Today, pharmaceutical manufacturers who elect to use "best" quality manufacturing practices should follow the second scenario in all cases.

SCENARIO ONE – Focus On The USP's Post-Release LIMITS Range For ALL Units

Given: **a)** no units can be outside of the USP's "75 % to 125 %" range and **b)** today's production batches of dosage units often exceed one million (1,000,000) units, the maximum dispersion that can be tolerated is one that has a risk of units outside of the **USP**'s "75 % to 125 %" range that is significantly less than one (1) in one million.

Since the effective risk for a +/- 6 sigma interval in a uniform distribution is still "3.4 units per million" (3.4 per 1,000,000) units in a batch, a choice of a +/- 6.5 sigma for that range would seem to be prudent for the batch.

Under this choice, the upper limit on the relative $\text{sigma}_{\text{batch}}$ is 3.846153846.

To correct this $\text{sigma}_{\text{batch}}$ limit to an $\text{RSD}_{\text{"batch"}}$ limit (RSD limit for a ***batch-representative sample***), one should divide $\text{sigma}_{\text{batch}}$ by approximately (1 + the variability fraction uncertainty introduced by the measuring of a small number of units [or ~ {1 + "f"}) or ([(30) / 12 sigma] / ~ {1 + P}).

Presuming: a) a 95 % confidence level is needed (the least justifiable confidence level for batches larger than about 10,000 units) **and b) the valid results from a tested sample of *any* size drawn from a *representative sampling of* that *batch* can be *representative* of the *batch*** (*a questionable assumption, at best, for sample sizes under 60 units*), the manufacturer can use the standard variability nomograph published in any of a number of statistics texts that address the uncertainty in the population variability based on the observed variability in the samples tested to determine the upper limit on $RSD_{\text{“batch”}}$, the following approximate $RSD_{\text{“batch”}}$ limits apply for a $sigma_{batch}$ of 3.846153846:

Number of “Representative” Units Tested	Approximate “f”	Effective Upper Limit “RSD” for Acceptance
10	0.45	2.65
30	0.25	3.08
60	0.18	3.26
200	0.083	3.55
750	0.05	3.66

SCENARIO TWO – Focus On The USP’s Post-Release EXPECTATION Range For All Units

For firms whose goal is to produce drug products that consist of units that meet the **USP**’s EXPECTATION range of “85 % to 115 %) [the “six sigma” firms], the upper limit on the expected RSD should be [(115 – 85) / 12 sigma] or a relative $sigma_{batch}$ of 2.5 divided by approximately (1 + the variability fraction uncertainty introduced by the measuring of a small number of units [or ~ {1 + “f”}) or [(30) / 12 sigma] / ~ {1 + P}. **Presuming: a) a 95 % confidence level is needed** (the least justifiable confidence level for batches larger than about 10,000 units) **and b) the valid results from a tested sample of *any* size drawn from a *representative sampling of* that *batch* can be *representative* of the *batch*** (*a questionable assumption, at best, for sample sizes under 60 units*), the manufacturer can use the standard variability nomograph published in any of a number of statistics texts that address the uncertainty in the population variability based on the observed variability in the samples tested, the following approximate RSD limits apply:

Number of “Representative” Units Tested	Approximate “f”	Effective Upper Limit “RSD” for Acceptance
10	0.45	1.72
30	0.25	2.00
60	0.18	2.12
200	0.083	2.31
750	0.05	2.38

No matter which of the two preceding (2) scenarios is proposed, several things are clear, including:

1. An $RSD_{\text{“batch”}}$ of “4” or “6” cannot be justified.
2. The maximum allowable $RSD_{\text{“batch”}}$ depends upon the sample size.

3. The RSDs proposed by this reviewer are consistent with ALL of the **USP**'s post-release "***any article in commerce***" criteria.

Moreover, the issue of the appropriate *size* (amount or number) for each *batch-representative sample* sampled needs to be addressed.

ESTABLISHING CGMP COMPLIANT INSPECTION (Sampling and Testing) PLANS

Fortunately, there are recognized 95%-confidence-level consensus standards that address the issue of the appropriate minimum sample numbers that those who drafted the draft guidance should have used as the basis for the sample numbers they proposed for the dosage units.

For variable factors, those standards documents are ISO 3951 and ANSI Z1.9 for batches of units that are tested.

In those standards, the **number** of ***representative samples*** that are required to be tested from a sampling of representative units is one that is of sufficient size to be ***batch representative***.

The requisite ***minimum number*** depends upon:

1. Size of the ***batch*** in terms of the theoretical number of units,
2. Whether or not the process variability is KNOWN,
3. Whether "NORMAL," "TIGHTENED," or "REDUCED" inspection is justifiable, and,
4. In some cases, the acceptance quality limit for the level of non-conforming units (AQL) that is appropriate for the units being tested.

[**Note:** In general, ***not less than 200 batch-representative units*** should be tested for active content **whenever** the ***batch size exceeds 150,000 dosage units*** **and** the ***process' true variability*** ("sigma") **is either not known or not knowable** (e.g., for initial performance qualification [evaluation qualification, conformance] batches and, *when all the critical physical and chemical properties for all components are not rigorously controlled*, all batches). The revised draft guidance submitted by this reviewer provides detailed hierarchical sampling plans that address the issues of sample size.]

If the dosage units are classified rather than tested, the appropriate US consensus standard is ANSI Z1.4 (which, for tablet and capsule batches, typically requires the evaluation of 800 or 1250 samples for the "NORMAL" inspection level).

Note: *For those who argue*, "testing more samples increases the risk of finding failing units," this reviewer would respond that that is the case **ONLY** when the *batch* being evaluated contains *failing units*.

Valid testing cannot find nonexistent units!

Firms not wishing to use the recognized applicable statistical consensus standards (ANSI/ASQC Z1.9 [or its ISO equivalent, ISO 3951 [or, for samples that are classified rather than tested, ANSI Z1.4]) should develop, and justify, the use of, a suitable *population predictive* evaluation plan that tests (or classifies)

the same number, or a larger number, of *batch-* or *lot- representative* sample units than those provided in the appropriate consensus standard.

This is the case because the consensus standards cited are based on the least number of units required to demonstrate *batch* or *lot acceptability* at the 95-% confidence level.

[**Note:** Firms wishing to have a higher confidence level in the acceptability of the batch or lot tested for its active content should either use a suitable validated statistical program to generate the number of samples required or consult a suitable statistics textbook that discusses designing variables acceptance sampling plans and follow the procedures outlined to determine the appropriate number of *representative* units to evaluate.]

FALSE PREMISE IN FDA'S PUBLISHED DRAFT GUIDANCE

Finally, the "statistical rationale … in Appendix 1" is based on a false premise that the **USP**'s RSD criteria are criteria that apply to a *representative sample* taken from the *batch*, when the reality is that the **USP**'s *post-release* criteria only apply to a non-representative grab sample taken from some small part of the batch.

"The number of samples specified in this guidance is excessive, and should be correlated with the batch size and/or the use of a well-designed study that would incorporate significant events into the 20 'planned locations' to lessen the burden of additional testing. The number of samples should be based on good science and be defined by the need for the statistical analysis of the data."

This reviewer rejects with the commenter's initial unsupported generalization, "(t)he number of samples specified in this guidance is excessive."

This reviewer agrees with the commenter that the number of samples tested "should be correlated with the batch size."

This reviewer agrees with the commenter that "(t)he number of samples should be based on good science" and again notes that, *for dosage units*, both ANSI and ISO standards provide recognized consensus standards that explicitly address the issue of the *minimum* number of *batch-representative sample units* that should be tested for batches of various sizes.

Though this reviewer does not know exactly what the commenter meant by the remark, "be defined by the need for the statistical analysis of the data," the CGMP regulations for finished pharmaceuticals (**21 CFR Part 211**) speak to the statistical analysis of the data for in-process materials and the drug product.

For example, in **21 CFR 211.110** "Sampling and testing of in-process materials and drug products," **21 CFR 211.110(b)** states (emphases added):
"**Valid in-process specifications** for such characteristics shall be consistent with drug product final specifications and **shall be derived from *previous acceptable process average and process variability estimates*** where possible and **determined by the application of suitable statistical procedures *where appropriate***. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications." [**Note:** The preamble to the 1978 revisions to **21 CFR Parts 210** and **211** states:

294. Several comments suggested deleting or revising the references in 211.110(b) to statistical methods for determining in-process specifications. Some comments said statistical procedures for this purpose were not well understood either by industry or by FDA. Others said other means of

determining in-process specifications should be allowed in addition to statistical means. One comment said manufacturers with tight limits and little batch variability would be penalized by this requirement. Another comment was that, because finished product specifications are arbitrarily derived, use of statistical techniques during in-process phases would be inappropriate. Several comments indicated that, in the case of new products or new manufacturers, there is no manufacturing history so other means of developing in-process specifications should be permitted.

The Commissioner is persuaded that there are other valid means of developing in-process specifications as alternatives to statistical methods. Therefore, the final regulation is revised to provide for application of statistical procedures, when appropriate. The Commissioner emphasizes, however, that in-process specifications must be meaningful in terms of achieving the desired finished product characteristics. Further, ***after product histories are developed***, the Commissioner encourages manufacturers to perform statistical analyses on their products and processes with a view to controlling batch-to-batch variability to the maximum extent possible.

295. Three comments suggested that 211.110(b) requires in-process testing, whether needed or not, but that paragraph (a) only requires testing in an optional sense.

The Commissioner recognizes that there are instances where the effect of variability during drug manufacturing phases cannot be predicted in relation to the drug product. Further, there may be instances where there are no suitable points, during in-process phases, to sample and test. The final regulations are reworded to clarify this.

296. One comment suggested that allowance be made in 211.110(b) for the use of in-process tests for adjustment purposes.

The Commissioner finds that specific references to in-process tests for adjustment purposes are unnecessary. The regulations provide flexibility to the manufacturer for establishing procedures for any appropriate in-process test and determining the significance of testing results."

Perhaps the preceding is the origin of their comment.

However, ***in today's world***, *current sound science requires that specifications be established using sound statistical analysis* – **thus, today, statistical analysis is required by CGMP**.]

In addition, in **21 CFR 211.165** "Testing and release for distribution," **21 CFR 211.165(d)** states (emphases added):

"**Acceptance criteria for the sampling and testing** conducted by the quality control unit **shall be adequate to assure that** batches of drug products meet each appropriate specification and **appropriate statistical quality control criteria** ***as a condition for their approval and release***. The **statistical quality control criteria shall include** ***appropriate acceptance levels and/or appropriate rejection levels***."

"There is no consideration provided for tablets that are not film-coated; uncoated tablet batches can fail the tighter in-process requirements for these new guidelines, but would pass the existing USP I/II criteria."

Since the draft guidance is for tablets and capsules and it addresses the formed in-process dosage units, including tablet cores (that, by definition, are uncoated tablets), the commenter's remark seems to be at odds with reality.

Moreover, the rest of the commenter's remark, "uncoated tablet batches can fail the tighter in-process requirements for these new guidelines, but would pass the existing USP I/II criteria" is but a repackaging of their prior remarks and, *for the reasons stated previously*, is similarly baseless.

"There is no consideration provided for blends and tablets that are greater than 50 % drub substance by weight. There should be a statement that these blends and tablets are excluded from this guidance."

With respect to this "general comments" paragraph, this reviewer notes:

1. **21 CFR 211.110** does not exclude such in-process materials drug products from compliance thereto.
2. The commenter presents **no** substantiating scientific evidence from real cases that such drug products cannot contain nonconforming units.
3. Since **21 CFR 211.110** applies to all variables that may "be responsible for causing variability in the characteristics of in-process material and the drug product," and, *as published*, the Agency's draft guidance purports to address the overall uniformity of the final blends and the tablet and capsule dosage units made therefrom, drug products with a high percentage of the active (50 % or more) may be more susceptible to uniformity failures for the minority components (lubricants, disintegrants, and other release control agents) that may or do adversely affect the safety and/or efficacy of some percentage of the dosage units in each batch.

Based on the preceding realities, this reviewer cannot support and the Agency should not support this paragraph's recommendation ("There should be a statement …") because:

1. Said recommendation is at odds with the clear regulations covering all finished pharmaceuticals as set forth in **21 CFR 211.110**, and
2. No substantiating body of data is submitted from a drug product that contains "50 %" active that, *based on the testing of not less than 300 batch-representative dosage units from each of not less than 10 batches*, clearly establishes that no tested units have an active level that is outside of the **USP**'s post-release EXPECTED range ("85 % to 115 %" of the target) and predicts, *at a confidence level of 99 % or higher*, there are NO units (less than 1 in 10^{12}) *in any batch* that are outside of the **USP**'s post-release LIMIT ("75 % to 125 %" of the target).

"Limited information is included in the guidance pertaining to sampling thieves/probes. A statement is needed to define various types and the need for a separate guidance on this topic."

This reviewer finds the commenter's remarks here to be, at best, misguided.

Since the industry and those that manufacture such "sampling thieves/probes" have much more experience with and understanding of "sampling thieves/probes" than the Agency, they, and not the Agency, should publish a definition of the various types of "sampling thieves/probes."

Moreover, *just as it is inappropriate for a guidance to reference other draft guidances that have not been (and may never be) finalized*, this reviewer finds that it is equally inappropriate for a guidance to include a "need" for another guidance.

Finally, the comments provided do not directly contribute to the issues at hand and, therefore, seem to be, *if they are not obstructive*, non-constructive.

"SPECIFIC COMMENTS

Section IV. B. Correlation of Powder Mix Uniformity with Stratified In-Process Dosage Unit data and Section VI. A. In-Process Dosage Unit Sampling and Analysis

Lines 150 and 254: The number of samples (20) required seem random; a well-designed study should provide information to support the number and locations of samples."

Since the number in question, number of sampling locations for the final blend "20" was provided by the PQRI, an industry sponsored organization and that "recommendation" was generated by "industry experts" who should have access to their firm's collective experience in this area, this reviewer does not understand the basis for the commenter's questioning the *recommended* "number" of sampling locations or for suggesting that "a well-designed study" is needed to "support the number" of sampling locations from a blender.

Moreover, since guidance does not and cannot require anything (guidance simply suggests a course of action), the draft does not state the "number of samples (20) required."

Finally, *from the general tenor of the commenter's remarks*, it seems that the commenter feels that "20" is too large a number.

As to the issue of "locations," this reviewer agrees with the commenter that the general locations suggested in the guidance are not appropriate because they are proposed to be sampling from those areas where the least uniform blend is "expected" to be found while the CGMP regulations CLEARLY require that in-process and drug product samples MUST be REPRESENTATIVE of the batch – not just from the areas where the blend is thought to be least uniform.

"Section V. EXHIBIT/VALIDATION BATCH POWDER MIX HOMOGENEITY

Lines 220-223: If powder blend is shown not to be a predictor of the in process dosage form uniformity and efforts to ID a source of error in blend sampling cannot be identified, then blend sampling should be eliminated for a given product."

First, in keeping with the improved terminology used in the 12 March 2004 revision to Sec. 490.100, "Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval," of the FDA's compliance policy guide (CPG 7132c.08), this reviewer now recommends that the title for Section "V" should be revised to read as follows:

"**Section V. INITIAL CONFORMANCE-BATCH POWDER MIX HOMOGENEITY**"

to conform to the terminology that this revised FDA policy has adopted for the process validation of drug products.

Factually, the draft text in **Lines 220-223** states:

"Sampling errors may occur in some powder blends, sampling devices, and techniques that make it impractical to evaluate adequacy of mix using only the blend data. In such cases, we recommend that you use in-process dosage unit data in conjunction with blend sample data to evaluate blend uniformity."

In this reviewer's comments to this section, the draft text in **Lines 220-223** was stricken "~~Sampling errors may occur in some powder blends, sampling devices, and techniques that make it impractical to evaluate adequacy of mix using only the blend data. In such cases, we recommend that you use in-process dosage unit data in conjunction with blend sample data to evaluate blend uniformity~~," based on the following rationale:

> "This commenter does NOT agree with this paragraph because, as the commenter's remarks on the taking and testing of unbiased samples indicate, it is possible to take and test unbiased sample aliquots in most every instance.
>
> When the blender size or configuration precludes directly sampling from it and/or introduces sample-level biases that cannot be overcome by increasing sample size, a valid IBC-container-sampling plan can ***and should*** be developed and used to overcome such problems.
>
> Because this is increasingly the case, this commenter recommends that the Agency include and establish the validity of a sampling plan that the Agency would recommend to the industry.
>
> If the root cause of observed non-uniformity problems is ***solely*** related to the sampling device used and/or the sample techniques used, sound science requires that the manufacturer change either or both in a manner that eliminates such biases."
>
> ***If the root cause of the observed non-uniformity is related to the mechanical stability of the blended powder, then this reviewer strongly recommends that the formulation itself and the blending procedures used to arrive at the offending blend should be revisited and improved until the physical stability of the blend itself becomes an insignificant contributor to the non-uniformity observed***.

With the inclusion of the added words, "***and should***" and "***solely***," and the last sentence added, this reviewer stands behind his prior assessment.

The commenter's recommended course of "***sampling plan***" actions are <u>neither</u> ***scientifically sound*** <u>nor</u> ***appropriate*** as required by **21 CFR 211.160 (b)** ["Laboratory controls shall include the establishment of **scientifically sound and appropriate** specifications, standards, **sampling plans**, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include: …"].

As such their recommendations are clearly at odds with the CGMP regulations and, *on that basis alone*, should <u>not</u> be incorporated into this guidance.

Factually, IF "powder blend is shown not to be a predictor of the in process dosage form uniformity," THEN it is, or should be, obvious that that manufacturing process does <u>not</u> meet the requirement ***minimums*** of **21 CFR Part 211**.

In such cases, the firm should (*as a recent article in the March 2004 issue of* ***Pharmaceutical Technology*** [T. P. Garcia, A. Carella, and V. Pensa, "Identification of Factors Decreasing the Homogeneity of Blend and Tablet Uniformity," pages 110, 112, 114, 116, 118, and 120-123] *clearly demonstrates*)

improve their manufacturing process to the point that the uniformity of the final blend is a predictor of the uniformity of the formed dosage units.

Because the CGMP regulations in **21 CFR 211.110(c)** clearly state:
"In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods," any commenter who recommends "blend sampling should be eliminated for a given product" is recommending the Agency publish something that seems to be clearly at odds with the 1988 Supreme Court decision that ruled that it was not legal for the Agency or any Agency official to publish documents that are at odds with any clear binding regulation.

Further, IF, as stated by the commenter (emphases added) "**efforts** to ID a source of error in blend sampling **cannot be identified**," THEN such firm should be appropriately sanctioned for making no effort to "ID a source of error in blend sampling."

Even if the commenter meant to say, "if … the source of error in blend sampling cannot be identified," this reviewer would reject their premise because: **a)** it is not scientifically supportable, **b)** ignores the reality that it is incumbent on the manufacturer to comply with all of the CGMP regulations including all of those set forth in **21 CFR 211.110**, and **c)** flies in the face of the body of published information, including the most recent article in the March 2004 issue of ***Pharmaceutical Technology*** written by supposedly competent Pfizer personnel who should be peers to the commenter.

For all of the preceding reasons, the commenter's proposed changes should be rejected.

"Section VI. B. Criteria to Meet the *Readily Pass* Classification

Lines 278-281: In these rows, use the mean of the data with a range, instead of the target strength/label claim. (In the beginning of the document there is a comment that this guidance is about uniformity, not potency. If the FDA wants to address uniformity, now is a great opportunity to separate content assay from CU assay.)"

At best, the commenter is attempting to equate "batch uniformity" with mathematical precision.

Moreover, their position flies in the face of the post-release reality in which the requirements are clearly require the "target/label claim" to be considered because the **USP**'s post-release requirements for active content are CLEARLY percentage ranges of the target or label claim.

The commenter's parenthetical remark is even less well reasoned because, *unless the methods used are biased and the dosage-unit-sized samples tested for active content are not, as they are required to be,* ***batch representative***, the mean of the *batch-representative sample*'s results when said sample is tested for active content should be exactly same as the mean of a ***representative-sample-sized*** assay within the experimental uncertainty of the test and testing.

Since the CGMP regulations, governing the **pre-release** sampling and testing of samples CLEARLY require that all in-process (**21 CFR 211.160(b)(2)**) and drug-product (**21 CFR 211.160(b)(3)**) samples MUST be ***representative***, one should not and cannot attempt to, separate **pre-release** "content assay from the CU assay" as the commenter proposes.

Thus, the commenter's suggestions should be ignored.

"Section VIII. A. Applications Not Yet Approved

Line 430: The correct reference for Drug Product Specification in the CTD is 3.2.P.5.1."

This reviewer agrees that the section citation should be corrected, but not necessarily as the commenter has noted.

"APPENDIX 1
COMPARISON OF ACCEPTANCE PROBABILITIES FOR DIFFERENT CRITERIA AND SAMPLING SCHEMES

SAMPLING SCHEMES AND OPERATING CHARACTERISTIC CURVES TO COMPARE THE CRITERIA WITHIN EACH SCHEME

Operating characteristic (OC) curves for a given sampling plan, allow an assessment of the probability of acceptance when applied to a batch with a given level of quality. …"

First of all, the commenter's remarks contain at least one false premise.

At a minimum, the commenter should have written:
"Operating characteristic (OC) curves for a given "***unbiased statistical sampling plan from a normal distribution***" allow an assessment of the probability of acceptance when applied to a batch with a given level of quality."

Because, as the **USP's *General Notices*** clearly states, the **USP**'s procedures are NOT "statistical sampling plans," ALL of the comparison examples that follow are obviously NOT *scientifically sound* and, at best, misleading (*if not an outright knowing effort to misrepresent factual reality to support patently invalid criteria that, instead of being based on sound inspection science and, where possible, supported by the appropriate recognized consensus standards [ANSI an/or ISO], are simply what the commenter wants to be able to get away with*).

Further, the "***stratified sampling" plans*** proposed ***are inherently biased*** **and do NOT ensure** that the ***samples*** sampled or tested **are** truly ***representative*** of the ***batch*** (as required by **21 CFR 211.160(b)**).

Because the samples taken are not sufficient in size (amount or number) to be considered generally *representative* of the *batch*, all that the statistical machinations do with certainty is estimate the theoretical fraction of samples that would pass given the assumptions used, and not the percentage of *batches* that truly meet the CGMP requirements in a manner that assures that **all** of the *dosage units* in *each batch* will probably (*at a confidence level of 95 % of higher*), *if tested post release*, meet all of the **USP** *post-release* requirements for said batches of dosage units.

Finally, there is ample commentary (by other commenters and this reviewer) that clearly indicates that the distribution of the active level in the materials discussed in this Draft is not a normal distribution and (*by this reviewer*) the assumptions used by the commenter are not appropriate (e.g., the "75 % to 125 %" and "85 % to 115 %" ranges used) or, *though required by CGMP*, not required to be attained by this draft guidance (e.g., mean of not less than 100 % [**21 CFR 211.101(a)**]).

Thus, the Agency should reject this appendix because the information in it is based on false premises – **a)** the **USP**'s sampling plans for uniformity are not the ***statistical sampling plans*** that they MUST be before any such comparisons should even be attempted, **b)** the sampling plans proposed in this draft guidance are inherently biased and do not, therefore, provide the requisite ***representative samples***, and **c)** the assumptions made by the commenter are either not valid on their face or at odds with the specifications proposed in the draft guidance.

Moreover, *to non-statisticians*, the appendix obscures the reality that one can have little confidence (<20 % when not more than 30 units are tested) that the test results from the testing of that few samples are, *provided the samples tested* are *representative* (*a condition that is, at best, not ensured by the inspection plans proposed*), adequately predictive of the distribution of active contents in the dosage units that make up *each batch*.

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

C-03 Comments By Eli Lilly and Company, Posted 9 March 2004

In an attempt to be thorough, Lilly's formal comments were submitted in three parts. To facilitate their review, the Agency chose to publish them through an HTML cover page that divided Lilly's submission into four (4) parts as follows:

"03D-0493
C 3
Volume 1
Cover Letter
Appendix A - The Original Guidance with Tracked (Highlighted) Editorial Suggestions
Appendix B - Matrix of Rationale for Each of the Editorial Suggestions
Appendix C - Clean Copy of the Guidance with the Incorporated Suggestions (for ease of reading)"

The Lilly "Cover Letter" begins by stating:

"Eli Lilly and Company has completed a thorough review of the Draft Guidance for Industry on Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment; Assessment, issued by the Food and Drug Administration under docket No 2003D-0493. Lilly has a few general areas of comment with regards to this proposal."

The reviewed Lilly comments are as follows:

"**MAJOR COMMENTS ON DRAFT GUIDANCE**

This guidance provides a new approach for ensuring compliance to the GMP 21 CFR 211.110(a)(3), which Lilly and other companies have historically controlled through development, blend uniformity validation, and routine monitoring of dosage units and in-process weight control. We believe that this is an important guidance because it provides a new systematic approach for demonstrating blend uniformity when implementation of process analytical technology (PAT) is impractical or not possible."

This reviewer first notes that Lilly begins by mischaracterizing **21 CFR 211.110(a)(3)** as "GMP" rather than ***properly*** labeling it a "CGMP" regulation.

Second, *since failure to comply with any of the minimums of any of the applicable CGMP regulations set forth in **21 CFR Parts 211** renders the drug products so manufactured adulterated (under **21 U.S.C. 351(a)(2)(B)**) and subjects those drug products and those persons who manufactured then subject to penalty under law*, Lilly's assertion that "Lilly and other companies have historically controlled through development, blend uniformity validation, and routine monitoring of dosage units and in-process weight control" seems to be an admission by Lilly that they, *and other unidentified companies of which Lilly has knowledge*, have been and are knowingly (as that term is defined in **21 U.S.C. 321(bb)**) engaged in the manufacture of adulterated drug products.

Third, *while this reviewer would agree that the proposed draft is a* "new systematic approach," the Agency's published draft guidance:

A. Is not *scientifically sound* and ***appropriate*** (as required by **21 CFR 211.160(b)** [emphases added], "Laboratory controls shall include the ***establishment of scientifically sound and appropriate*** specifications, standards, ***sampling plans***, and ***test procedures*** designed to assure that components, drug product containers, closures, ***in-process materials***, labeling, and **drug products conform to appropriate standards of identity, strength, quality, and purity.**"),

B. Does not meet the "**uniformity and integrity**" "**of each batch**" requirements set forth in **21 CFR 211.110** (emphases added):

"Sec. 211.110 Sampling and testing of in-process materials and drug products.

(a) **To assure batch uniformity and integrity of drug products**, written **procedures shall be established and followed that describe** the **in-process controls, and tests**, or examinations **to be conducted on appropriate samples of in-process materials of each batch**. **Such** control **procedures shall be established to monitor** the **output** and **to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product**. **Such** control **procedures shall include**, but are not limited to, the following, where appropriate:

(1) Tablet or capsule weight variation;
(2) Disintegration time;
(3) Adequacy of mixing to assure uniformity and homogeneity;
(4) Dissolution time and rate;
(5) Clarity, completeness, or pH of solutions.

(b) **Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates** where possible and **determined by the application of suitable statistical procedures** where appropriate. Examination and **testing of samples shall assure that the drug product and in-process material conform to specifications**.

(c) **In-process materials shall be tested for identity**, **strength**, **quality**, and **purity** as appropriate, **and approved or rejected by the quality control unit**, **during the production process**, **e.g., at commencement or completion of significant phases** or after storage for long periods," and

C. Fails to provide adequate guidance for compliance with the example control procedure set forth **in 21 CFR 211.110(a)(3)**, "**Adequacy of mixing to assure uniformity and homogeneity.**"

Fourth, as written, the proposed draft does not ensure "blend uniformity" as Lilly asserts.

At best, it can only ensure the uniformity of the active or actives in the blend or the dosage units – the requirement set forth in **21 CFR 211.110(a)(3)** does not read, as the statements in Draft's guidance clearly imply, "**Adequacy of mixing to assure uniformity and homogeneity** *of* ***only*** *the active or actives in the formulation*."

[**Note:** Assuring that the active or actives are sufficiently uniform, *while necessary*, **is not *sufficient for compliance*** because that assurance does not assure that other ingredients critical to processing (e.g., lubricants) or performance (e.g., disintegrants and other release control agents, and "stabilizers") are adequately mixed (distributed). Unless the adequacy of mixing of ALL such is assured, the requirement ***minimum*** set forth in **21 CFR 211.110(a)(3) cannot** be fulfilled.]

"One area of concern is the timing allowed for manufacturers to meet the requirements of this guidance document. Numerous activities may be needed to be identified and implemented to be compliant with this guidance. Activities include stratified sampling, testing, training, revision of SOPs and manufacturing documents, and evaluation of data. In consideration of the above, Lilly believes a transition period (e.g., eighteen months) should be provided for in this guidance."

No Requirements – No Need To Allow For Timing

Since no guidance is binding and no guidance can or does impose any "requirements," this reviewer fails to find **any** validity in the commenter's assertion, "One area of concern is the timing allowed for manufacturers to meet the requirements of this guidance document."

This is the case because guidance is just that guidance and firms are free to comply with the CGMP minimums by whatever *scientifically sound* and *appropriate* CGMP-compliant procedures that they choose to establish.

CGMP Compliant?

If a firm is presently CGMP compliant, that firm should have no compelling need to do as the commenter's remarks indicate:
"Numerous activities may be needed to be identified and implemented to be compliant with this guidance."

If and when the Agency issues a final CGMP-conforming guidance, CGMP-compliant firms should not have any activity that, as the commenter asserts, "may be needed to be identified."

At most, all that such CGMP-compliant firms may wish to do is modify one or more of their current CGMP-compliant activities.

Though Lilly states, "Activities include stratified sampling, testing, training, revision of SOPs and manufacturing documents, and evaluation of data," the suggested activity, "**stratified sampling**," should not be included **BECAUSE**, as the draft guidance defines "**stratified sampling**," said sampling does not, ***as the CGMP in-process minimums require***, **provide a *representative sample*** (as that term is defined in **21 CFR 210.3(b)(21)**, "Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled" – not that "accurately portrays" *some part of* "the material being sampled").

Thus, this reviewer strongly recommends that the Agency reject Lilly's request, "In consideration of the above, Lilly believes a transition period (e.g., eighteen months) should be provided for in this guidance," for the clear and compelling reasons presented.

"Finally, the scope of the guidance is broader that was discussed by PQRI in that it includes products that would currently be controlled by USP Weight Variation. This would include 'products containing 50 mg or more of an active ingredient comprising 50 % or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule content'[1]. For drug products which fall into this USP category, we believe analytical testing of the dosage units is unnecessary and would negatively offset the cost savings expected form the proposal as a whole.'

[1] 2004 USP vol 27, p2396"

Contrary to the commenter's statement, "products that would currently be controlled by USP Weight Variation", **none** of the **USP**'s *post-release* uniformity requirement specifications are directly applicable to the *pre-release* or *release* active uniformity requirements established **in 21 CFR 211.110**, **21 CFR 211.160**, **21**

CFR 211.165, **21 CFR 211.166**, or **21 CFR 211.167** as they apply to in-process materials, including the in-process formed dosage units, and the drug product that is not in commerce.

This is the case because the CGMP regulations ***require:*** **a)** specifications *appropriate to* a ***representative sample*** *of* the *batch* **and b)** the testing of a ***representative sample*** from the *batch* – the **USP**'s post-release uniformity specifications apply to the **USP *article***, a grab sample, and, as the **USP** states, the **USP**'s sampling plans are not statistical sampling plans and they do not require the ***article*** sampled and tested to be ***representative*** of the *batch*.

In addition, the CGMP regulation ***minimums*** set forth in **21 CFR 211.110** are the controlling requirements and, as written, apply to each batch of ***all*** drug products.

There is no valid sound science that would support not assuring that such drug products are adequately uniform before they are released *because there will be no post-release evaluations* – don't assure uniformity because the post-release **USP** requirements do not check for active uniformity – an approach that is not only anti-quality and illegal but also ignores the need for the assessment of the uniformity of each "mix" for *other critical variable factors*.

The applicable "**WEIGHT VARIATION**" subsections, "UNCOATED AND FILM-COATED TABLETS," and "HARD CAPSULES," end the same way, "**assuming homogeneous distribution of the active ingredient**."

When the **USP** permits homogeneity to be assumed, it is more important that the pre-release testing assure that the **USP**'s post-release assumption condition is met than when the post-release **USP** testing requires a content uniformity determination.

Based on Lilly's stated belief, "we believe analytical testing of the dosage units is unnecessary", it would again seem that Lilly is knowingly operating in a manner that does not comply with the CGMP regulations.

Finally, in 1998, the US Supreme Court held that the Agency has no latitude with respect to issuing any written statement which conflicts with the ***clear*** requirements of any binding CGMP regulation.

For all of the reasons cited, this reviewer recommends that Lilly's remarks (concerning the in-process testing of blends and dosage units) be rejected by the Agency because they are clearly conflict with both sound inspection science and the law or are, in the case of Lilly's "timing" issue, inappropriate.

"**PROCESS FEEDBACK**

Lilly found the PQRI forum to be a very efficient and effective way to generate a strong working proposal on blend uniformity. As a result of the participation of topic leaders in the FDA leaders, academia, and industry a draft recommendation, based on solid science and public feedback , was submitted to the Agency."

Since Lilly is a founding sponsor and strong supporter of the PQRI, this reviewer is not surprised that the commenter "found the PQRI forum to be a very efficient and effective way to generate a strong working proposal on blend uniformity."

However, *as this reviewer's repeated **unanswered** submissions concerning the PQRI's "recommendation" to Agency and the PQRI as well as an "accepted then refused" Letter to the Editor" concerning the PQRI's "recommendation" that the PDA refused to publish even though they had no problem publishing the PQRI's "recommendation" **attest***, the "recommendation" submitted to the Agency" had little in the way of ***scientifically sound*** public feedback.

Moreover, contrary to Lilly's assertion that said recommendation is "based on solid science," this reviewer continues to find that the PQRI's "draft recommendation" and the Agency's published draft guidance:

a. Are not based on sound science, and
b. Repeatedly ignore clear applicable **CGMP regulations**.

"Since the process of working with PQRI was so successful, Lilly supports the use of the PQRI committee to work through other technical regulatory issues in the future."

Until and unless the PQRI's recommendations:

- Are truly based on sound science and the appropriate recognized consensus standards (where they are applicable),
- Conform to the clear requirements of the CGMP regulations,
- Are truly open to the non-industry public at no more than a nominal cost, and
- Support the publication of, and respond to, dissenting views,

this reviewer must recommend that the Agency not accept any proposal submitted by the PQRI.

"**EDITORIAL SUGGESTIONS**

The basic concepts and approach in this guidance document are viewed by Lilly as sound and based on good science."

For the reasons stated, this reviewer knows:

- Neither the basic concepts nor the approach in the published draft guidance document are *scientifically sound*.
- The published draft guidance ignores:
  - The clear requirements of most, if not all, of the CGMP regulation ***minimums*** that apply to in-process materials and in-process drug products,
  - Recognized CGMP definitions and both the national (ANSI Z1.9) and international (ISO 3951) consensus standards that address discrete-unit sampling procedures and tables for inspection by variables for percent nonconforming (and active content is a variable), and are, therefore, clearly applicable, and
  - Sound inspection science.

Thus, this reviewer continues to find that the "science" reportedly used is flawed.

"While the overall flow and verbiage in the document are acceptable, Lilly has provided a number of editorial suggestions to this document, which we believe will enhance the understanding, clarity, and flow of the document. These editorial suggestions do not change the document's content. Three appendices are included in helping understand the editorial suggestions.

- Appendix A This is the original Guidance with tracked (highlighted) editorial suggestions
- Appendix B A matrix with rationale for each of the editorial suggestions
- Appendix C A clean copy of the Guidance with the incorporated suggestions for ease of reading"

Contrary to the commenter's statement, this reviewer has found that many of the changes suggested do, in fact, *materially* change not only the content of the document but also the guidance that is being suggested.

Because of manner in which Lilly responded, this reviewer has chosen to review Appendix A and, where necessary, consult Appendix B's rationales.

Review of Lilly's Appendix A

Lines 22-28, "~~This guidance describes the procedures for assessing powder mix adequacy, correlating in-process dosage unit test results with powder mix test results, and establishing the initial criteria for control procedures used in routine manufacturing~~. This guidance describes a control procedure for the manufacturer to routinely assess the adequacy of powder mix/drug uniformity by the use of stratified in-process dosage unit sampling and testing instead of routine blend sampling, provided that a feasibility assessment is made prior to implementation of the stratified sampling approach."

First, Lilly's proposed alternative statement is not nearly the same as the draft guidance's language.

Second, because *stratified sampling*, as defined in this guidance, does not generate a ***representative sample*** (as *defined by* **21 CFR 210.3(b)(21)** and *required by* **21 CFR 211.160(b)(2)**), *stratified sampling* is not appropriate for compliance with **21 CFR 211.110**.

Third, assessing the active content variability is necessary but not sufficient to assess the adequacy of powder/mix uniformity because any assessment of the "Adequacy of mixing to assure uniformity and homogeneity" must also determine that the materials being evaluated is appropriate with respect to not only the active or actives but also the lubricants, disintegrants and other release-control components, and "stabilizers" whose test values monitor the output and "validate the performance of those manufacturing processes may be responsible for causing variability in the characteristics of in-process material and the drug product" as required in **21 CFR 211.110(a)**.

Fourth, contrary to the commenter's assertion, a feasibility study is not a permitted alternative to the clear "***each batch***" requirements: **a)** to "assure batch uniformity and integrity of drug products" and **b)** "to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product" set forth in **21 CFR 211.110(a)**.

Fifth, as written, **21 CFR 211.110** requires that uniformity assessment be made for *each batch* at the "**at commencement or completion of significant phases**" in the manufacturing of the drug product and not, as the commenter would have it, at the commencement or completion of ***some*** of the significant phases of the production of each batch manufactured.

Therefore, the commenter's proposal is violative on its face as it proposes to do less than the clear ***minimums*** established in the in-process CGMP regulations for drug products.

For all of the preceding reasons, the commenter's suggestions here should be rejected by the Agency.

Lines 44-46, "In response to industry concerns regarding regulations for demonstrating the adequacy on in-process powder mixing, the FDA published a draft guidance for industry containing new approaches for~~on~~ blend uniformity analysis in August 1999.[2]"

The commenter's proposed change attempts to mischaracterize the 1999 draft guidance as "containing new approaches for" blend uniformity analysis when factually the guidance simply proposed a means by which firms could comply with the preexisting (*since 1979*) clear CGMP requirements concerning establishing the uniformity of the blends in the manufacture of *each batch* of drug product.

Based on the preceding reality, this reviewer recommends that the commenter's suggested change should be rejected because it attempts to distort reality.

Lines 65-72, "~~*Stratified sampling*~~Stratified sampling of dosage units is ~~the~~ a process of ~~sampling dosage units at predefined intervals and~~ collecting representative samples from ~~specifically~~ predefined, targeted locations in the ~~compression/filling operation~~dosage unit forming process that have the greatest potential to yield extreme high~~s~~ and low~~s in~~ test results. These test results are used to monitor the manufacturing process output ~~that is~~from the locations most responsible for ~~causing~~ finished product variability. ~~The test results~~Stratified sampling of dosage units can be used to ~~develop a single control procedure to~~ ensure adequate powder mix and in some cases, uniform content in finished products."

Rather than attempt to address the individual changes and their impact, this reviewer only addresses the commenter's "editorial suggestions" that, contrary to the firm's assertion, do materially "change the document's content"

First, the commenter redefines "*Stratified sampling*" in a manner that limits it to the dosage units.

Second, the commenter's definition does not, *as their modified text still states*, permit the "collecting of representative samples" (as the term representative sample is defined in **21 CFR 210.3(b)(21)**) of the "**each batch**" as required by **21 CFR 211.110(a)**.

The commenter then uses this "modified" definition to falsely assert that said definition, "Stratified sampling of dosage units," can be used to "ensure adequate powder mix," *whatever that means*, and not the "**assure uniformity and integrity**" of the blends and the formed dosage units as **21 CFR 211.110** requires.

For all of the preceding reasons, the commenter's suggestions should be rejected because said suggestions omit the "blend" manufacturing phases from

uniformity assessments proposed even though the in-process CGMP regulations clearly covers these *significant phases* of the production process (**21 CFR 211.110(c)**).

Moreover, *as this reviewer has repeatedly pointed out*, in the science of inspection (sampling and sample evaluation) the more appropriate term for the periodic sampling across a batch is "*Dynamic sampling*," as that term is defined in this reviewer's formal comments to this docket as opposed to "*Static sampling*," where the sampling is done after a process step has been completed.

The adjective "*stratified*" means layered and, as described, sampling during the production is not layered.

Moreover, the use of the word "*locations*" is misleading because sampling while the dosage units are being formed is time based rather than location based.

If the commenter truly wishes to perform *stratified sampling* of the formed units, the commenter should change the definition to require the sampling to be delayed until all of the dosage units have been formed and containerized and, then, proceed as the definition suggests, to select samples from different locations from specified layers in each container of dosage units.

Since the commenter has not changed the "sampling" definition as outlined by this reviewer, the appropriate description of what the commenter proposes is the "dynamic sampling of dosage units" and all references to such sampling plans should be so defined.

Lines 79-81, " After readily passing (Section V.B.2) the validation requirements, products that are allowed to meet USP Uniformity of Dosage Units by weight variation are exempted from future routine blend testing requirements."

The commenter's suggested course of action here should be summarily rejected because it is contrary to the *clear* requirement ***minimums*** of the in-process CGMP regulations set forth in **21 CFR Part 211**.

Moreover, *because such have not been released into commerce*, the **USP**'s "Uniformity of Dosage Units" chapter most certainly does not apply to the non-discrete blend samples or the discrete in-process formed dosage units in *any* drug product batch.

Lines 88-93, "

- ~~Correlate~~ Compare the stratified sample data with the powder blend data.
- Assess powder mix uniformity.
- ~~Correlate~~ Compare the stratified in-process dosage unit ~~sample~~ data with the finished dosage unit data ~~and assess~~to determine whether in-process samples may be used to assess uniformity of content."

This reviewer agrees with the commenter that the better characterization of the *data contrasts* is as a *comparison* rather than as a *correlation*.

However, because there is no assurance that the samples being compared are *population representative*, this reviewer knows that such comparisons are, at

best, biased and, unless there is some valid physical connection between the each sampled final-blend location and a corresponding sampling point for the formed dosage units, the valid comparisons are limited to comparing the overall statistically estimated batch characteristics of the final blend to the like projected batch characteristics of the dosage units formed from said final blend.

Footnote 8, "[8] In ~~August~~ September …"

This reviewer agrees with this correction.

Lines "95-97," "Some f~~F~~ormulations ~~with extremely low dose and/or high potency~~ may call for more rigorous sampling than that described in this guidance to assess the uniformity of powder blends or the uniformity of content of the finished dosage units."

This reviewer continues to object to both the original wording and the commenter's suggested simplification because all formulations intended for use in tablet and capsule forming operations require "more rigorous sampling than that described in this guidance" IF that guidance is to be CGMP compliant.

This is the case because **21 CFR 211.160(b)** requires that the firm take and test a ***representative sample*** for all in-process and drug product samplings and this draft guidance does NOT – the "stratified sampling plan proposed does not provide a ***representative sample*** (as defined by **21 CFR 210.3(b)(21)**) – calling a sample *representative* does not make it a ***representative sample***.

Lines 109-111, "When using the methods described in this guidance, ~~certain data or~~ trends may be observed in the data. We recommend that manufacturers scientifically evaluate ~~these types of~~ research data for trends, ~~to~~ determining ~~e~~ if they affect the quality of a product and, if so, how."

Again the commenter's "editorial suggestions" have materially altered the meaning of the draft guidance in a manner that reduces, and attempts to marginalize, the evaluation of the data by changing the focus from "certain data or trends" to "trends."

Based on the preceding, this reviewer cannot support the changes suggested by this commenter.

Lines 119-121, "**IV. ~~CORRELATION OF~~EVALUATION OF POWDER MIX AND IN-PROCESS STRATIFIED SAMPLING DURING PROCESS DEVELOPMENT ~~WITH POWDER MIX AND FINISHED PRODUCT~~**"

This reviewer objects to the title revision because it not only materially changes the scope of this section but it also improperly limits it to "**DURING PROCESS DEVELOPMENT** even though the in-process CGMP regulation ***minimums*** for drug products do not support that limitation.

At most, the word "**CORRELATION**" could be changed to "**COMPARISON**" because again this alternative term is the more appropriate and more general one that properly characterizes the section it heads.

Therefore, the commenter's changes should NOT be made.

Lines 123-132, "If you plan …"

This reviewer objects to the revisions proposed because they not only materially change the scope of the guidance provided in this section but they also improperly limits it to development when the in-process CGMP regulation ***minimums*** for drug products do not provide for such limitations.

Therefore, *because the law proscribes the FDA's publishing guidance that conflicts with any* ***clear*** *regulation*, the suggested changes should not be made.

Lines 136-139, "As part of development, we recommend that you assess critical events in the blending process and determine appropriate sampling techniques for demonstrating a validated blending process. As part of that evaluation, w~~W~~e recommend the assessment of powder mix uniformity using the following procedures:"

Because the proposed commenter's "editorial suggestions" materially change the guidance and are not compatible with the requirement ***minimums*** of the applicable CGMP regulations, they should not be made.

If the Agency wishes to incorporate a statement such as the commenter proposes in this guidance, this reviewer then recommends the following alternative wording be used:

"As part of development, we recommend that you assess ~~critical events in the~~ all aspects of the components, formulation, and blending process and ~~determine~~ develop appropriate sampling and sample evaluation techniques for demonstrating a ~~validated~~ a valid blending process."

As the CGMP regulations for finished pharmaceuticals clearly indicate, ***validation is a journey*** and **not**, as the commenter's "validated blending process" phraseology treats it, *a destination*.

Lines 140-147, "

- Conduct blend analysis on batches by ~~extensively~~ sampling the mix in the blender[9] and/or intermediate bulk containers (IBCs). When sampling from a blender, identify sampling locations[10] to represent potential areas of poor blending. For example, in tumbling blenders such as V-blenders, double cones, or drum mixers, samples should be selected from at least two depths along the axis of the blender. For convective blenders such as a ribbon blender, a special effort should be made to implement uniform volumetric sampling to include the corners and discharge area.

[9] Sampling can be done from other equipment that is being used to mix the blend, such as a fluid bed.

[10] Typically, at least 10 locations for tumbling blenders and at least 20 locations for convective blenders are selected."

First, this reviewer sees no need to strike "extensively" as the commenter proposes because that is what firms should do.

Moreover, this reviewer finds much of the rest of the commenter's "editorial suggestions" to be at odds with sound inspection science and the CGMP requirements for a *population representative sample*.

In addition, this reviewer finds it strange indeed that the commenter chose to add extensive verbiage to this bullet point about sampling from the blender but

elected to add no similar "extensive" guidance for sampling from containers (IBCs).

This reviewer would have thought that such a sagacious commenter would have taken the "opportunity" provided by **21 CFR 211.110(c)** to define the completion of the final blending phase as the "completion of the transfer of the final blend into its IBCs" and propose that beyond the lab-scale, sampling should be from the IBC(s) in which it resides or is transferred and held under quarantine prior to quality unit approval for dosage-unit formation.

Had the commenter done this, then not only would the commenter have eliminated the "scale" problems associated with production-scale equipment but also, were the commenter to carefully design the sampling plans for both the final blend in IBC(s) and the dosage units formed from it, actually be able to validly compare the uniformity of the final blend in each IBC container to the corresponding uniformity of the dosage units formed from that portion of the blend. [**Note:** For example, presuming a process conformance batch study, the final blend resides in 9, about "50-kg" drums and the final blend sampling plans takes one unbiased multiple-dose sample from the top middle and bottom of each drum. Unbiased duplicate aliquots are tested from each sample (54 evaluations) and as they should, not only do the results verify that the blend is adequately uniform, the results confirm that the active level in the "top" of container "n" is about the same as the active level in the "bottom" of container "n+1." After quality unit release, and machine tooling set up and operational verification, the contents of each container are carefully transferred into the dosage-forming system's feed hopper in a manner that preserves the order of the materials in the container so that, with respect to the container, the material in the hopper ranges from container-1 "bottom" at the "hopper's "top" to container-1 "top" at the hopper's bottom. The machine is started and, after initial adjustment and steady state on-target weight, and other processing specifications are met, an appropriate multiple-unit [4 X number of dosage forming stations] "start" sample is taken and labeled "IBC-1 Top DUS-Start." The next dynamic sample point is set when the hopper is half full, the next dosage unit sample is taken and labeled "IBC-1 Mid Time-Point 1 (TP-1)" and the second container is loaded into the hopper. When the next dosage-unit sampling point is reached (when the last of IBC-1 {IBC-1 Bottom} is being tableted), the dosage sample is taken and labeled "IBC-1 Bot/IBC-2 Top TP-2" and so on, until the ninth drum has been loaded and the hopper rundown reaches the IBC-9 Middle and the sample labeled "IBC-9 Middle End," and a hoper rundown study is started and samples labeled "RNDN-1" through "RNDN-5" are taken at the "40%", "30," "20, "10 %," and "5 %" Hopper levels. Since there were no interruptions in processing, you should end up with a start, "16" time-point, end, and "5" rundown/runout samples. The lab then randomly selects 12 dosage units from each sampling point and weighs then in a manner that preserves the link between the weight and the tablet number and sampling point. After weighing all of the samples (216 in all}, randomly selects and analyzes sets of 24 from across the set sampled. When all 216 results are available, then the dosage units' results from each sampling point can be linked to the blend location (for one-half the samples) or locations (the other half). The weight-corrected relative active-content results for the 12 dosage units from the half of the sampling points that are clearly from the material from a given container (the "-Mid TP 1, 3, 5, 7, 9, 11, 13, and 15, and the "-Mid End" samples) can clearly be compared to the results from the duplicate-aliquots from each of the 9 "IBC-n Middle" "final blend" samples. The data for the entire set can be used to establish the "as is" uniformity of the dosage units. Since lab studies have previously confirmed that there is no significant difference in the active level in the freshly formed dosage units, the firm can validly omit active uniformity assessment from the set of assessments of uniformity required for the in-process finished dosage units – which minimally must be tested for the active availability uniformity and any other critical variable factor that is not fixed until the finished dosage unit are generated. If the data from all initial full-scale conformance batches indicate that the active uniformity data (range, distribution, mean, RSD, skew) for all such are within narrow limits the same and all are acceptable, then a thorough review of all of the data may permit the dosage-unit inspection program to initially evaluate only on-fourth of the samples required for the full set (216) in this case. Similarly, provided the blends show comparable

uniformity and uniformity patterns, you may be able to scientifically justify inspecting the bottom and middle of the first drum, the mid points from drums 2-8 and the middle and top of the last drum (11 locations instead of 27 locations). In such cases, you may also be able to justify reducing your sampling frequency to capture a "Start," the Mid-Container regions for drums 1 through 8 and, as an "End" sample, the mid for drum 9 (10 sampling points). Though, in such cases, the number of samples collected at each time point would to be doubled, the number dosage-unit samples tested for active in each sample sampled would only need to increase from 12 per sampling point to 20 per sampling point. This revised routine inspection plan would then form the basis for the firm's "normal" inspection plan for the active in the blend and the dosage units and said plan would preserve the capability to compare the batch-representative results from the blend to the batch-representative results from the dosage units produced from the blend. When, after producing not less than 10 consecutive full-scale batches that had acceptable uniformity for the active and all other critical variable factors, you should be able to adopt a staged inspection plan (see this reviewers comments to PhRMA for an example of such) that appropriately reduces the number of dosage units that you should evaluate initially while preserving the sampling point pattern/final blend connection. However, in every case, all of the requisite sampling points should be sampled and the size of the dosage units sampled should be the full size. This plan would then be your basis "reduced" sampling plan.]

If additional detail is needed as to where and how to sample, this reviewer suggests that it: **a)** be provided elsewhere and **b)** also address the sampling from IBCs (the example in the reviewer's previous "Note" could be used as a starting point).

From this reviewer's extensive experience with the inspection of blend samples from "V," split pot, slant-cone, ribbon, and blade mixers, this reviewer finds:

A. It very odd indeed that the locations specified for the blenders do not include sampling from the wall/blend boundary layer or the air/blend interface.

B. That the minimum number of levels is, *except for laboratory-scale equipment*, insufficient and at odds with the implicitly applicable requirements provided in the regulations for the sampling of components (**21 CFR 211.84(c)(4)** which states, "Samples shall be collected in accordance with the following procedures: … (4) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.").

C. At odds, with the reviewer's experience that:

- **i.** Three-level sampling was the minimum for blenders larger than about 5 ft^3 in working volume,
- **ii.** For V blenders, the sample plan should appropriately offset the intermediate levels (not the top or the bottom levels) in each arm,
- **iii.** For ribbon and other fixed-shell blenders with rotating mixing elements showing any wear (groves or other non-uniformities in the shell or uneven wear in the blades), a sampling grid pattern needs to be laid out for each level that ensures that includes additional sampling locations (in addition to those for the ends, wall, discharge-valve well [at two levels] and random samples from the bulk blend) across the blender from those areas where the blade gap is least, average, and largest. [**Note:** In this reviewer's experience, firms should avoid using such blenders in most cases.]

In addition, the "blender" sampling plans proposed, "potential areas of poor blending" is not only at odds with sound inspection science but also does not conform to the "representative sample" requirements of the CGMP regulations.

Based on all of the preceding, this reviewer cannot support the commenter's "editorial suggestions" and would suggest that this text not be modified as the commenter proposes.

Lines 148-149, "

- Identify appropriate blending time and speed ranges, dead spot in blenders, and locations of segregation in IBCs. ~~Determine sampling errors~~."

While this reviewer has no problem with the commenter's "editorial suggestions" here, this reviewer would *again* recommend that this bullet be revised to state the positive as follows:

"• Develop controls on component specifications, blender loading and blending regimens that eliminate 'dead spots' in the blender and 'segregation' on storage in the IBCs."

Lines 150-155, "

- Define the effects of sample ~~size~~ quantity (e.g., …"

While the preferred term for a non-discrete collection is amount (since quantity is more typically associated with a number of discrete items), this reviewer finds that the commenter's suggested change is an improvement over the more ambiguous term "size" in the published Draft.

However, this reviewer again recommends that this bullet be revised to read,

"• Develop a sampling plan that:
a) Samples aliquots of sufficient amount that they are not significantly biased by the sampling procedure used and, at a minimum, are at least five (5) times the amount needed for all testing when physical characteristic tests are performed or, *when no physical characteristic tests are required*, ten (10) times that needed for all possible testing,
b) Takes a *batch-representative* set of samples from *each batch*,
c) Subsamples unbiased unit-does or smaller aliquots from each sample sampled for all chemical tests with duplicate aliquots from at least 30 % of the samples.
d) Tests sufficient subsample aliquots from each sample to provide sufficient data to characterize the batch, and
e) Evaluates the results obtained against *scientifically sound* and *appropriate specifications* and *batch acceptance criteria* that, at the last step, must be appropriately inside of the *specifications* and *acceptance criteria* for the *batch* of dosage units by at least the amount of non-uniformity that can be contributed by the allowed variability in the weight of the dosage units."

Line 156, "~~□ Design blend sampling plans and evaluate them using appropriate statistical analyses."~~

Because the commenter's "editorial suggestion" is at odds with sound science, the requirements of **21 CFR 211.160(a)** that require that any sampling plans must be established, and the in-process requirements (**21 CFR 211.110**) for the testing of a *representative sample* at the commencement or completion of significant phases of manufacturing, this reviewer objects to the deletion proposed.

Moreover, this reviewer would again propose a slight revision to the Draft as follows:

"• Design blend-sampling plans and evaluate them using ~~appropriate~~ *scientifically sound* statistical analyses *that are appropriate for non-discrete materials*."

Lines 157-162, "

- Quantitatively ~~measure any~~evaluate the variability that is present among the samples. Attribute the sample variability to either lack of uniformity of the blend or sampling error. ~~Significant~~ High within-location variance in the blend data can be an indication of one factor or a combination of factors such as inadequacy of blend mix, sampling error,[11] analytical error, or agglomeration. [12, 13] ~~Significant~~ High between-location variance in the blend data can indicate that the blending operation is inadequate."

While this reviewer has no significant problems in the commenter's "editorial suggestions" here, this reviewer recommends that this bullet should be revised to read as follows:

"• Provided all of the observed average values for the multiple measurements made on each aliquot tested are within the scientifically sound and appropriate predetermined limits specified, at the 95-% confidence level or higher, **estimate** the following "apparent values" for the following parameters: batch mean, batch variance, the test variance, the within-location variability, the between-location variability, and the "random" error component for each factor evaluated. Use these values to estimate the true batch mean and limit values and the minimum "process" capability for the batch. Use that data to develop the appropriate control charts for that process. When there is significant between-location variance in the blend data, the manufacture needs to ascertain what combination of improved controls (on the physical properties of the components, formulation, blender loading, blending regimen, and, where the blender is unloaded into IBCs, blender unloading, IBC storage and IBC sampling) are needed to render the blend uniform."

In addition, this reviewer knows that a bullet point is needed for the setting of specifications appropriate to the performance of the blending process.

To accomplish this, this reviewer recommends adding the following bullet:

"• When blend developmental studies reach the point that the projected population distribution within the *batch* is approximately constant and all sample results are well within their appropriate limits, use the statistical data developed from the final-stage developmental batches to establish appropriate interim final *blend specifications* for the *representative samples tested* as well as the *predicted population limits*."

Lines 163-165,"

- Based upon the results of the development work, identify a sampling and testing plan appropriate for the validation of mix uniformity (e.g., sampling locations, sample quantity, appropriate statistical analyses)."

The commenter's "editorial suggestions" here is a positive contribution to the draft guidance.

However, to be fully CGMP-compliant, this reviewer suggests that the commenter's suggestions should be modified as follows:

"• Based upon the results of the development work, identify *and establish* a sampling and testing plan appropriate for the validation of mix uniformity (e.g., sampling locations, sample quantity, appropriate statistical analyses) *for* ***each batch*** *manufactured*."

Lines 167-168, "**B. ~~Correlation~~ ~~Evaluation~~ Comparison of Powder Mix Active-Uniformity Data ~~with~~ ~~using~~ With ~~Stratified~~ Dynamically Sampled In-Process Dosage-Unit Active-Uniformity Data** "

This reviewer does not agree with the "editorial suggestions" proposed by the commenter.

First, *if this Draft conforms to the CGMP regulations as it should*, the published draft's text "discusses" dynamically gathering a *batch-representative* in-process dosage-unit *sample*, evaluating a sufficient number of *batch representative* units for each critical factor and comparing the batch's *representative-sample* statistics for the dosage-unit results found to those of the batch-representative blend sample set's data.

Thus, this section discusses a comparison

Second, to maintain parallel construction, the construction "Uniformity Data" should be used in both instances where "Data" is used.

Because the section discusses a comparison, "with" is the appropriate word – not "using," but this reviewer suggests changing "with" to "With " to improve the grammatical correctness of the title because "with" has an equal weight with respect to the other capitalized words in the title.

In addition, because a valid "*as the product is produced*" sampling plan requires a *dynamic sampling* of a *process-representative number* of dosage units at the start, a sufficient number of intermediate points, and the end of production such that *each sampling* is *time-point representative* and the *aggregate number of samples sampled* is ***batch representative***" and the "stratified sampling" plan proposed does not satisfy the aforesaid criteria, the word "**Stratified**" was appropriately replaced with the phrase "**Dynamically Sampled**" to align the title with the CGMP-compliant *sampling plan* proposed by this reviewer for sampling during production.

Lines 170-173, "As part of development, we recommend that you assess the in-process dosage unit data to identify locations throughout the forming operation that have a higher risk of producing failing finished product uniformity of the content results due to segregation or poor powder mix. We recommend the following steps ~~for correlation~~:"

This reviewer finds the commenter's "editorial suggestions" here to be problematic.

The commenter's suggestions *improperly* reduce the requirements for assessing each batch's blend uniformity and integrity to only assessing the data for active content.

Moreover, during development, the goal should be to reduce the blend variability to the point that, within the allowed variability, the batch is uniform and there are no identifiable locations where there is a poor powder mix or significant segregation.

With the preceding in mind and mindful of the title, this reviewer suggests changing the commenter's proposed text to read as follows:

"As part of development, we recommend that you assess the in-process dosage unit data and develop the formulation and blending steps used until there are no identifiable ~~to identify~~ locations throughout the forming operation that have a higher risk of producing failing finished product uniformity ~~of the content results due to~~ for all critical variable factors in the blend that can be traced to segregation or poor powder mix. When development efforts are successful in producing batches that consistently meet the aforementioned goals, the firm should finalize the inspection plan for each critical variable factor in the in-process and commence marking the initial full-scale operational batch to verify the validity of the firm's manufacturing steps up through the manufacture of the freshly formed dosage units. We recommend the following steps ~~for correlation~~ for that evaluation:"

Lines 175-179, "

- Conduct periodic sampling and testing of the in-process dosage units by sampling them at defined intervals and locations throughout the compression or filling process. ~~Use a~~A minimum of 20 appropriately spaced in-process dosage unit sampling points is recommended. There should be at least 7 samples taken[14] from each locations for a total minimum of at least 140 samples."

[14] A minimum of 3 (of the 7) dosage units per location should be assayed.

This reviewer cannot agree with the original text or the commenter's "editorial suggestions" because the texts conflict with the fundamental precepts of inspection science and/or the clear in-process CGMP requirements.

Instead of the existing text, this reviewer proposes the following scientifically sound and CGMP-compliant alternative:

"• Conduct periodic sampling and testing of the in-process dosage units by sampling them at defined points throughout the compression or filling process. For developmental studies, use a sampling plan that begins with a start sample and ends with a end of forming sample, contains sufficient sampling points so that no more than 5 % of the batch is formed into dosage units between successive sampling points, and provides for the taking of additional "restart" samples whenever there is a stoppage in the dosage forming process. *At each sampling point,* at least one *sample unit* must be taken from *each* dosage-forming station in the dosage forming system being used to ensure that a ***batch-representative sample*** is taken as required by **21 CFR 211.160(b)(2)**. *At a minimum*, the firm should collect *at least* three times the *number* of *sample units* required to perform ***all*** the in-process evaluations (e.g., active content, content availability, impurity, water, etc.), which are required by the in-process CGMP regulations for drug products, on a ***batch-representative sample***. These studies should be conducted using, as appropriate, process developmental or process conformance batches, or by using routine manufacturing batches for approved products."

Lines 180-184, "

- Take at least 7 samples from each additional location to further assess each significant event,[15] such as filling or emptying of hoppers and IBCs, start and end of the compression or filling process and equipment shutdown. ~~This may be accomplished using process developmental batches, validation batches, or by using routine manufacturing batches for approved products~~.

[15] A *significant event* is any operation during the solid dosage production process that can affect the integrity of the in-process materials – see section IX Glossary."

Though this reviewer agrees with the need for points to cover "significant events," in general the preceding is also neither *scientifically sound* nor CGMP-compliant and, *as the reviewer's proposed text suggests*, would include start of compression or capsule filling and tooling or other maintenance disruptions that trigger a restart in the first bullet.

Again, the taking of only seven-unit samples is, in general, scientifically unsupportable.

Moreover, the commenter's "editorial suggestion" for deleting the second sentence in this bullet is unsupportable because these studies may, for a variety of reasons, need to be conducted on an existing product or one in the initial full-scale validation phase as well as for those drug products in an earlier stage of development.

However, as the reviewer's proposed text states, the second sentence belongs at the end of the first bullet

Typically, during start up, successive "all station" sample sets should be taken and their conformance to the established set up criteria (typically, weight, dimension, hardness (for tablets) or closure integrity (for capsules), and, in some cases, disintegration) monitored until the production equipment appears to the operator to be meeting its set-up criteria (in some cases, a "pre-start" sample may be taken).

At that point, the "start" sample should be taken and, based on the nominal unit production speed and batch size, the sampling times for the time points should be estimated.

The preceding procedure should also be used whenever an interruption requires a maintenance step that changes the nature of the dosage forming system (such as a tooling replacement) except that each such sample taken should be considered a "restart" sample.

After the normal "end of compression" or "end of filling" sample units are taken, a hopper run-down study similar to the start up one should be conducted until the unit-forming system looses weight control (in some cases, a "post-end" sample may be collected just after the "end" sample to verify that control was maintained after the "end" sample was taken.

While the testing of appropriate units from: **a)** the starting up to "start" point, **b)** restarting up to "restart" point, and **c)** the "end of processing" sample to the loss of weight control should be used to verify the validity of the controls established to define the "in control" points in the dosage-forming step, the "significant event"

"restart" sample sets must be included in and augment the number of samples required to be tested to establish the uniformity of the batch.

Thus, based on the applicable recognized consensus standards for determining the acceptable quality (ANSI and/or ISO) for processes where the true process mean and variance are either unknown, or, because of a lack of sufficiently *rigorous* component and/or process controls, "unknowable," a firm would need to test not less than 200 batch-representative units or, for the recommended scenario, start, 10+ time-point samples, end sample, "n" restart samples, and "m" other study samples about 10 units, selected at random, from each sample collected for each critical variable factor in the drug product.

Based on the preceding, this reviewer suggest changing the second bullet to read:

"• As outlined above, take not less than three times the number of samples as the number required for all testing from "each additional ~~location~~ sampling point to further assess each additional significant event,[15] such as filling or emptying of hoppers and IBCs, and machine runout after the end (cutoff point) for the forming of acceptable dosage units.

[15] A *significant event* is any operation during the solid dosage production process, including component acceptance evaluation, that ~~can~~ may affect the uniformity or integrity of the in-process materials – see section IX Glossary."

Lines 185-186, "

- Significant events may also include observations or changes from one batch to another (e.g., batch scale-up and observations of undesirable trends in previous batch data."

This commenter strikes this bullet point because it is <u>not</u> pertinent to the case at hand where the tablet data are to be compared with the previous final blend data for the same batch.

This must be the case because, *given the lack of rigorous controls on the physical properties of the components used*, the blend results from one batch <u>cannot</u> be validly compared to the tablet results from some other batch.

Based on the preceding, this reviewer also recommends striking the third bullet as follows:

- ~~Significant events may also include observations or changes from one batch to another (e.g., batch scale-up and observations of undesirable trends in previous batch data)~~.

Lines 187-192, "

- -Prepare a summary of the data <u>(</u>and analysis<u>) identifying the significant events observed in the manufacturing process that may impact blend uniformity. From this, identify 20 stratified sampling locations that may be used to verify or validate blend uniformity[16].</u> ~~used to correlate the stratifies sampling locations with significant events in the blending process. We recommend that you submit this summary with the application as described in section VIII of this guidance."~~

This reviewer cannot agree with either the original or the commenter's suggested alternative because neither is *scientifically sound* nor CGMP compliant.

For reasons similar to those stated for the previous bullet, this reviewer does not understand the rationale for including "discrete event" issues in a section providing guidance for a comparison of the blend data from one batch to the dosage-unit data from that same batch as no such direct comparison is valid under the sampling plans proposed in the Draft.

Since the individual results cannot be directly compared, the comparison must be made on a population statistics inferential basis.

In addition, all that one can do (with respect the uniformity of the batches' blend as estimated by the weight-corrected values for each of the critical variable factors that must be assessed under the CGMP regulations) is determine that subset of samplings, including the "start and "end" points, that reliably provides the "same" estimates of variability as the complete set of sampling points and, *provided the full sets have been evaluated for a sufficient number of batches (that number is proportional to the change in uniformity observed [as the uniformity increases {RSD decreases})*, establish that subset of sampling points that can be routinely used for the uniformity of the formed dosage units.

Further a comparison of the weight-corrected uniformity data's relative mean and RSD to the blend data's uniformity data's relative mean, variance, kurtosis, higher derivative terms and projected limits, *provided both data populations are from the results obtained from the testing of unbiased batch-representative samples*, can only properly be used to estimate the divergence between the means, variances, kurtoses, higher derivatives and projected limits, if any, that is attributable to the transfer and forming operations occurring after the blend sampling.

Provided a sufficient number of *batch-representative samples* have been evaluated, one can confidently predict, *from the relative variability estimates observed (RSDs) for the uncorrected data*, the probable level of formed dosage units that do not conform to the specifications established.

However, lacking independent estimates of the transport, transfer, and forming, variances, one can only make a biased estimate of the estimated upper limit for the uniformities for the critical variable factors in the blends.

Based on all of the above, this reviewer recommends that the fourth bullet point be revised to read as follows:

"Prepare a summary of the data *including the specific content values (content values corrected to the target unit or unit-fill weight) for each tablet tested and the corresponding statistical estimates derived therefrom minimally at the 95-% confidence level* ~~and analysis used to correlate the stratified sampling locations with significant events in the blending process.~~ We recommend you submit this summary with the application as described in section VIII of this guidance."

Lines 193-194, "

- Compare the powder mix uniformity data with the in-process dosage-unit uniformity data described above.

Though the commenter's "editorial suggestions" do improve the grammatical correctness of the statement made, this reviewer finds that the statement suggests a scientifically unsound "apples and oranges" comparison.

Since, *unless there is a way to track the blend location tested through the dosage-unit forming step and take a dosage-unit sample that is known to be related to the blend (typically, this can only be done when the final blend sampling is from the IBCs)*, there is no scientifically valid way to *directly* compare an individual result for a given blend sample sampled from a non-discrete population to a given individual specific result sampled from a transformed discrete population for a given dosage unit; statistics must be used to compare the probable aggregate distributional properties of the two process steps (final blend and dosage-unit formation).

The Draft should explicitly address the preceding reality.

Also, to make the comparison an "apples to apples" comparison, the specific-content-value statistics estimated for the batch of units (not the observed-content-value statistics) for the dosage unit values should be compared to the corresponding estimated statistical properties of the weight-based blend data.

With all the preceding in mind, this reviewer suggest that the text should be revised to read:

"• Compare the powder mix uniformity ~~data~~ data's *distributional statistics* (the mean, standard deviation and probable population limits) *obtained using the approaches outlined in Subsection A* with the corresponding in-process dosage-unit statistical population inferential values (the mean, standard deviation and probable population limits) derived from the weight-corrected response result values obtained using the procedures outlined in this subsection. Provided all results are within their expected ranges and the statistics predict that the populations (blend and in-process dosage units) are within their targeted ranges, use the results obtained to appropriately update**: a)** the *interim* blend specifications **and b)** the *interim* in-process dosage-unit specifications."

Lines 195-200, "

- Investigate any discrepancies observed between powder mix and dosage-unit data and establish *probable* root causes. At least one trouble-shooting guide is available that may be helpful with this task.[~~13~~ 17] Possible corrections may range from going back to formulation development to improve powder characteristics to process optimization. Sampling problems may also be ~~negated~~ ~~obviated~~ addressed by use of alternate state-of-the-art methods of *in situ* real-time sampling and analysis (e.g., P.A.T.).

[~~13~~17] JK Prescott, TJ Garcia, "A Solid Dosage and Blend Content Uniformity Troubleshooting Diagram," Pharm. Technol., 25 (3):68-88, 2001."

This reviewer does not agree with the replacement of "negated" by "obviated" and suggests that the more appropriate substitution, if any is required, would be to

replace "negated" with "addressed" because the feasibility of using this approach and the outcomes from using it are, *a priori*, not knowable.

In addition, this reviewer suggests inserting the word "*probable*" before "root causes" because the valid comparisons are inherently uncertain estimates of the true population values.

Finally, this reviewer suggests adding the following bullets to address the proper setting of the appropriate in-process acceptance specifications for the final blend and in-process dosage units and reporting issues, respectively:

"
- When all the development studies have been completed for the formulation used to manufacture the final blend and the in-process dosage units, and all the blend and in-process formed dosage units results track each other, fall within their expectation windows, and predict that all of the untested blend and in-process formed dosage units will meet the *interim* specification limits established for the final blend and the freshly formed dosage units, establish tentative dosage unit specifications for the final-development stage batches.
- Prepare an interim summary of the data, *interim* specifications, and analysis used to conclude that: **a)** the blend inspection (sampling and evaluation) **and b)** the *dynamic* in-process sampling and sample evaluation provides adequate assurance of uniformity of the finished product."

Lines 202-215, "~~**C. Correlation of Stratified In-process Samples with the Finished Product**~~

"~~We recommend the following steps~~:

- ~~Conduct testing for uniform content of the finished product using an appropriate procedure or as specified in the Abbreviated New Drug Application (ANDA) or the New Drug Application (NDA) for approved products.~~
- ~~Compare the results of stratified in-process dosage unit analysis with uniform content of the finished dosage units from the previous step. This analysis should be done without weight correction.~~
- ~~Prepare a summary of the data and analysis used to conclude that the stratified in-process sampling provides assurance of uniform content of the finished product. We recommend you submit this summary with the application as described in section VIII of this guidance.~~"

This reviewer cannot agree with the commenter's "editorial suggestion" to delete this entire subsection of the guidance because the requisite studies may find that there are significant differences between the formed dosage units and the finished dosage units for some of the critical variable factors (active content, active availability, impurity, water, etc.) that the in-process CGMP regulations require the firm to monitor and validate for *each batch*.

If there are such differences, the firm should determine what they are during the development of the drug product.

Instead, this reviewer recommends the following changes:

For the title:

"**C. Comparison of the Results From the Dynamically Sampled Representative In-process Samples To the Representative Finished Product Samples Tested**"

For the first bullet point:

"• Conduct testing for uniformity ~~content of~~ the finished product on *batch-representative samples* using ~~an~~ appropriate CGMP-compliant procedures *(21 CFR 211.160(b)(3), 21 CFR 211.165(d), and, for controlled-release dosage forms, 21 CFR 211.167(c)*) or, *when the manufacturer's approved application or license specifies a larger batch-representative number is required to be tested, ~~as~~ the larger number* specified in the Abbreviated New Drug Application (ANDA) or the New Drug Application (NDA) for approved products."

The CGMP regulations ***minimums*** clearly require that *batch-representative samples* be sampled and tested since doing less renders the batch adulterated.

Given the CGMP requirement ***minimums*** and the 1988 Supreme Court decision, Berkovitz v. USA, the Agency's guidance cannot legally suggest doing less than the CGMP regulation ***minimums*** clearly require.

For bullet point 2:

"• Compare the *statistical uniformity inferences derived from the* results ~~of stratified~~ *observed for the dynamically sampled* in-process dosage unit analysis *from the previous step* ~~with uniform content~~ *to the corresponding statistical uniformity inferences derived from the representative sample results from ~~of~~* the finished dosage units ~~from the previous~~ tested for uniformity in *this* step. This comparative statistical analysis ~~should~~ **must** be done without weight correction.[~~14~~ 18]

[~~14~~ 18] Weight correction is a mathematical correction to ~~eliminate~~ *correct for* the effect of ~~potentially variable~~ *the* tablet weight on ~~measurement of mix adequacy~~ *measured tablet content values* —see Glossary, Section IX."

The comparisons should be between the statistical inferences (e.g., means, variances, kurtoses, other derivative statistical values, and the probable ranges) and not between the values observed.

For some critical variable factors (*e.g., active availability and water*) that the in-process CGMP regulations require the manufacturer to monitor, the statistical inferences may indicate that there is a significant bias between the probable values for the in-process dosage units and the finished dosage units even when the results obtained are valid *batch-representative* sets.

Based on the preceding realities, this reviewer has suggested the revisions shown.

With respect to the published Draft's definition of the term "weight correction," by definition, a "correction" does not eliminate anything; it "corrects" an observed factor (*in this case the observed active content value*) for the effect on that factor of some partially correlated confounding factor (*in this case, dosage-unit weight*).

Moreover, the correction presumes that: **a)** the content level depends upon the weight of the dosage-unit core or, *in the case of capsules*, the dosage-unit fill **and b)** this weight dependency can be removed by multiplying each active level by the target unit weight divided the observed weight.

[**Note:** Practically, this is obviously much easier to do for tablet cores than it is for the fill weight in the case of capsules.]

For bullet point 3:

"• Prepare a summary of the data, *interim* specifications and analysis used to conclude that the ~~stratified~~ *dynamic* in-process sampling provides assurance of uniformity ~~content~~ of the finished product. We *recommend* you submit this summary with the application as described in section VIII of this guidance."

As these terms are defined, ***dynamic sampling*** takes *batch-representative samples* and complies with this CGMP requirement for the in-process (**21 CFR 211.160(b)(2)**) and drug product (**21 CFR 211.160(b)(3)**) samples while "*stratified sampling*" neither takes *batch-representative samples* nor complies with said CGMP requirement.

In addition, the CGMP regulations require the manufacturer to determine the uniformity and integrity of each batch for all critical variable factors, including but not limited to, active content, active availability, weight, and, as appropriate, water, impurities, etc.

Lines 219-232, "**V EVALUATION OF EXHIBIT/VALIDA~~T~~ATION BATCH POWDER MIX HOMOGENEITY**

~~This section describes sampling and testing the powder mix of exhibit and process validation batches used to support implementing the stratified sampling method described in this guidance.~~

We recommend that during the manufacture of exhibit and process validation batches, you assess the uniformity of the powder blend~~,~~ and the in-process dosage units~~, and the finished product~~ to ensure adequacy of blend uniformity ~~independently~~. ~~We recommend you use the following steps to identify sampling locations and acceptance criteria prior to the manufacture of the exhibit and/or validation batches~~. We recommend that the sampling locations for blend and stratified samples should be identified per Section IV. This comparison of powder mix uniformity and stratified in-process dosage unit uniformity is completed before establishing the criteria and controls for routine manufacturing."

This reviewer cannot support the commenter's supposedly "editorial suggestions" because they both do not comply with the applicable CGMP and, contrary to the commenter's assertion, do materially change the guidance proposed.

This reviewer would propose the following alternative:

"**V EVALUATION OF THE UNIFORMITY OF INITIAL PROCESS CONFORMANCE BATCHES**

This section describes sampling and testing the final powder mix, in-process *dynamically sampled dosage units, and the finished dosage units* of the PROCESS CONFORMANCE batches used to support implementing the *representative*

sample ~~stratified~~ sampling and sample evaluation ~~method~~ *plans* described in this guidance

We recommend that during the manufacture of *all initial process conformance* ~~exhibit and process validation~~ batches, you assess the uniformity of the powder blend, the in-process dosage units, and the finished product independently. We recommend you use the following steps to identify sampling locations and acceptance criteria prior to the manufacture of ~~the exhibit and/or validation~~ *any process conformance* batches.[18A]

[18A] This is described in Section IV of this guidance."

Because, as per **21 CFR 211.110(a)**, all batches validate the process and, therefore, it is CLEAR that ***all batches*** are "validation batches."

Since it is clear that this section of the draft guidance is intended to address only the *initial process validation batches* that the Agency has *recently* (12 March 2004) formally labeled as initial process "conformance batches," this reviewer has modified the text accordingly.

Lines 234-244, "**A. Demonstrating Powder Mix Uniformity**

This section describes sampling and testing the powder mix of ~~exhibit and process validation~~*process conformance* batches used to support implementing the ~~stratified~~ sampling ~~method~~ *plans* described in this guidance. ~~Some powder blends may present unacceptable safety risk or be physically impractical (e.g., large V-blender) when directly sampled.~~In cases where the direct sampling from the blender presents an unacceptable risk for direct sampling or such sampling is physically impractical (e.g., the manufacture should justify and use and alternative procedure for monitoring and validating the uniformity and integrity of such blends. Unless the toxicity of the active presents an unacceptable safety risk to the persons doing the sampling and no robotic sampler is available, these justified sampling alternatives should be to sample from the IBCs using the sampling guidance provided in 21 CFR 211.84(c)(4) for the sampling of components as the *minimum* for the number of levels to sample from each container. In addition, as previously discussed, the samples sampled should be sampled, handled and subsampled (*aliquoted*) for testing in a manner that ensures that the samples tested are an unbiased set that is *representative* of the blend from which the sample set was taken. Each sample should be of sufficient amount to permit the testing of at least six (6) unbiased aliquots from it for each critical variable factor (active content, active availability, weight, identity, and, where indicated, water and other impurities) that was identified as having a significant variability in development studies conducted as per Section IV.A. ~~Once described, these situations may justify an alternative procedure. In such~~ cases where sampling from the IBCs is not possible, process knowledge and data from indirect sampling combined with additional in-process dosage unit data may be adequate to demonstrate the ~~adequacy~~uniformity and integrity of the powder mix. In such cases, the scientifically sound and appropriate statistical ~~D~~data analysis used to justify using these alternate procedures should be described in a summary report that ~~is~~must be maintained at the manufacturing facility, and should be: a) submitted as a part of any initial filing and b) referenced in any other filing appertaining thereto. ~~In general, we recommend:~~"

For all of the valid regulatory and sound inspection science reasons established previously, this reviewer recommends that the commenter's suggestions be modified as indicated in the text provided by this reviewer.

Lines 245-266, "

1. ~~Carefully identify at least 10 sampling locations in the blender to represent potential areas of poor blending~~ Identify at least 10 locations (the minimum number and location should be that which the developmental studies have proven to be sufficient to be *representative* of the *batch*) to collect powder blend samples. If taken from the blender, they should include areas that may be problematic in terms of uniform blend[19].

[19] ~~This~~ Developing an appropriate sampling and testing plan is described in Section IV.A of this guidance.

2. ~~Collect at least 3 replicate samples from each location. Samples should meet the following criteria:~~From each identified location, collect an unbiased sample of sufficient size to perform all the requisite testing in triplicate and still have an unbiased reserve for further evaluation of each critical variable factor in the blend should such be required

3. ~~Assay one sample per location, with the number of samples (n) ≥ 10. (n ≥ 20 for convective blender).~~ At a minimum, evaluate two unbiased unit-dose or smaller aliquots from each sample sampled for each critical variable factor that establishes the overall uniformity, or lack thereof, of the final blend. ~~Samples should meet the following criteria:~~

4. The samples results for each critical variable factor should meet *the scientifically sound* and *appropriate sample acceptance* and *batch acceptance criteria* established by the manufacturer during the development of the drug product.

   [**Note:** The manufacturer should submit all data, analyses of data and findings used to establish:
   a. which variable factors are the critical variable factors that establish overall uniformity,
   b. that the specifications established for each critical factor are scientifically sound and appropriate specifications for each batch of final blend, in-process dosage units, and finished dosage units and
   c. the specifications established do ensure, at a confidence level of not less than 95 %, that each and every article in a released batch, is predicted to meet the **USP**'s post-release criteria until the batch is in commerce for longer than the expiration date established for the marketed drug product

   to the Agency when they submit a filing that first references the specifications, or any change to the specifications when the manufacturer has previously not submitted said proves of validity to the Agency.]

5. When all exhibit-batch blend studies have been successfully completed, finalize all of the *interim* blend specifications and submit the *interim* specifications and a summary of the data and analysis used to support the setting thereof to the Agency with the application as described in section VIII of this guidance in Section VIII.

6. When all initial full-scale blend studies have been successfully completed, finalize the blend specifications, and submit said finalized blend specifications and a summary of the data and analysis used to support the setting thereof to the Agency with the application as described in section VIII of this guidance."

For all of the valid regulatory and sound inspection science reasons established previously, this reviewer recommends that the commenter's suggestions be modified as indicated.

"~~□ Assay one sample per location (number of samples (n) ≥ 10) (n = 20 for ribbon blender).~~

~~RSD (relative standard deviation) of all individual results ≤ 5.0 percent.~~

~~All individual results are within 10.0 percent (absolute) of the mean of the results~~."

This reviewer cannot support the setting of any specification limits in this guidance since, as written, this guidance addresses uniformity of the final blend, in-process formed dosage units and the finished drug-product dosage, and NOT just the uniformity of the active or actives contained therein.

It is, therefore, inappropriate to attempt to set guidance specifications ONLY for the uniformity of the active or actives contained therein.

In addition, neither this commenter nor the PQRI nor anyone in the Agency or the pharmaceutical industry, nor, as far as this reviewer has been able to ascertain, has submitted any *scientifically sound* body of evidence based on the testing of *batch representative samples* that supports the limits proposed in the draft.

Moreover, *to comply with the clear requirements set forth in* ***21 CFR 211.110(a)***, general drug-product uniformity guidance must address the uniformity of ALL critical variable factors – all of the variable factors that "may be responsible for causing variability in the characteristics of in-process material and the drug product" – and not just "content uniformity."

Finally, this reviewer again notes that this commenter has attempted to place the focus of this guidance on an example in **21 CFR 211.110, 21 CFR 211.110(a)(3)**, rather than, *as it should*, focusing on the general requirements, **21 CFR 211.110(a)** that:

A. Lists the example cited as part of a non-inclusive list of examples, and
B. Begins by clearly stating, "**To assure batch uniformity and integrity of drug products, …,**" the true goal of **21 CFR 211.110**.

Based on all of the preceding, this reviewer recommends that the Agency consider the preceding suggestions with respect to general uniformity and specification setting (and not those made by the reviewer in his formal response to Public Docket 2003D-0493), and change the Agency's published draft guidance appropriately so that it meets the clear requirements set forth in **21 CFR 211.110** for ***uniformity*** **in general**.

[**Note:** If the Agency decides to restrict the guidance provided to the ***uniformity of the active*** *or* ***actives*** in the blends, in-process dosage units, and finished dosage-unit drug product, then the Agency should consider using this reviewer's proposed Draft (titled "**Guidance for Industry Powder Blends And Dosage Units — In-Process Blend And Dosage Unit Inspection (Sampling And Evaluation) For Content Uniformity**) as the Agency's basis Draft (that this reviewer submitted to the Agency on 21 January 2004) or, *when it is available*, this reviewer's revised guidance, "**Guidance for Industry Powder Blends And Dosage Units — In-Process Blend And Dosage Unit Inspection**

(Sampling And Evaluation) For Active Uniformity DRAFT GUIDANCE – Second Revision)."]

Lines 267-278, "

If the samples do not meet these criteria, we recommend that you investigate the failure according to the flow chart in Attachment 1. ~~We also recommend that you not proceed any further with implementation of the methods described in this guidance until the criteria are met~~.Assay the remaining replicate blend samples. To aid in investigating the cause of failure, dosage form samples (7 from at least 20 locations) may be analyzed. These samples should have been obtained following the procedure described below in Section V.B. If the cause of the failure is identified as a mixing problem, we recommend that you do not proceed further with the implementation of the methods described in this guidance until a new mixing procedure is developed. If the cause of the failure is not because of mixing, but is attributed to sampling error or other problem(s) unrelated to the homogeneity of the blend, we recommend that you proceed with the evaluation of the dosage form ads described in Section V.B (see also Attachment 1). "

This reviewer cannot support the commenter's "editorial suggestions" for several reasons.

First, the commenter's suggested, "Assay the remaining replicate blend samples" is based on the fundamentally flawed sampling plan that again presumes that one need only determine the active level to establish that the final blend is sufficiently uniform, or not, when, in fact, other critical variable factors or their surrogates must also be measured.

Based on the preceding and in consideration of the requirement to assess the uniformity of other variable factors besides active content, it would seem that the general guidance furnished should address all of the variable factors that may be problematic, and not just the active or actives.

Second, the commenter's suggestions seem to clearly conflict with the CGMP regulations for in-process materials and drug products (**21 CFR 211.110(c)**, "In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods").

Unless the specifications established in development are met, how can the manufacturer's "quality control unit" approve that *final blend* as required by **21 CFR 211.110(c)**?

Isn't it a breach of CGMP to release ***failing*** *blends* to the next manufacturing phase, *dosage forming*?

Based on all of the preceding, this reviewer suggests the following alternate language, *provided* ***Attachment 1*** *is appropriately revised*:

"If the samples do not meet any one of ~~these~~ criteria established at the completion of the development phase for each critical variable factor, we recommend that you investigate the failure according to the flow chart in Attachment 1. We also recommend that you not proceed any further with implementation of the ~~methods~~ procedures described in this guidance until changes in the critical controls (*including those on the components used to produce the final blend*), formulation, process steps and processing can be proven to ensure that all the critical performance criteria are reliably met. Should the investigation find real evidence which indicates that the test results for the unbiased duplicate aliquots tested are suspect, then the

suspect samples should be retested by having two independent analysts (*whose competence in the test in question is recertified before proceeding*) evaluate an equal number of suspect samples and non-suspect samples by having each analyst sample and test two unbiased unit-dose, or smaller aliquots, from each sample (*suspect and non-suspect*) in the test set. IF: **a)** a cause for the discrepancies observed is proven, by factual evidence, to be sampling, analyst, or equipment error and/or **b)** the results of the additional evaluations ***clearly*** establish that the original results from one or more of the suspect samples are statistically non-sample-representative (*at a confidence level of not less than 99 %*), THEN, the original results may be excluded from the data set and the appropriately weighted results from the additional testing used to establish whether or not, the blend meets it pre-established specifications."

Lines 280-283, "~~Sampling errors may occur in some powder blends, sampling devices, and techniques that make it impractical to evaluate adequacy of mix using only the blend data. In such cases, we recommend that you use in-process dosage unit data in conjunction with blend sample data to evaluate blend uniformity~~."

This reviewer agrees with the commenter here.

Obviously, it is possible to take and test unbiased sample aliquots in most every instance.

When the blender size or configuration precludes directly sampling from it and/or introduces sample-level biases that cannot be overcome by increasing sample size, a valid IBC- sampling plan can be developed and used to overcome such problems.

Because this is increasingly the case, this reviewer recommends that the Agency include and establish the validity of an "IBCs" sampling plan that the Agency would recommend to the industry.

Lines 285-290, "~~Some powder blends may present unacceptable safety risk when directly sampled. The safety risk, once described, may justify an alternate procedure. In such cases, process knowledge and data from indirect sampling combined with additional in-process dosage unit data may be adequate to demonstrate the adequacy of the powder mix. Data analysis used to justify using these alternate procedures should be described in a summary report that is maintained at the manufacturing facility.~~"

This reviewer agrees with the commenter here because these issues have already been addressed in the "editorial suggestions" furnished by the commenter.

Lines 292-294, "As an alternative, you can substitute the procedures described in the PDA Technical Report No. 25, (see reference in footnote 11~~8~~) to ensure that the blend is uniform and that the method meets or exceeds the criteria described above.

This reviewer cannot agree with the commenter's decision to leave this text in the draft.

That is the case because the procedures in ***PDA Technical Report No. 25*** are not *scientifically sound* and do not meet the clear requirement ***minimums*** established in the CGMP regulations for drug products.

Moreover, based on the 1988 Supreme Court decision cited previously, it is not legal for any person in the Agency to recommend the use of any procedure that does not at least meet the applicable clear CGMP regulation ***minimums***.

For the preceding reasons, this paragraph should be removed from the Draft and this reviewer recommends that it be stricken as follows:

~~"As an alternative, you can substitute the procedures described in the PDA Technical Report No. 25, (see reference in footnote 8) to ensure that the blend is uniform and that the method meets or exceeds the criteria described above~~."

Lines 295-297, "

B. Assessment and Classification of Stratified In-Process Dosage Unit Uniformity

This reviewer cannot agree with the commenter's "editorial suggestions" here for several compelling reasons:

1. Properly, the dosage-unit sampling is not stratified (layered) but dynamic.
2. Because there are a variety of critical variable factors whose uniformity must be established and the *scientifically sound* and *appropriate* statistically derived limits for each of the factors may be different in different formulations, this reviewer is unaware of any valid general classification scheme that the Agency might propose.
3. As far as this reviewer can ascertain, there exists no published body of batch *representative data* where sufficient *batch-representative samples* have been evaluated so that the data validly predicts the general population distributions at a confidence level of at least 95 % for various target levels of each critical variable factor in a general formulation matrix that covers even the most common approved formulations.
4. Based on the Section V header and the parallels between what should be done here and what is recommended in IV.B, an assessment of the in-process data and a comparison to the blend data is what should be done.
5. The title should be similar to the title in IV.B.

Based on the preceding, this reviewer recommends changing the title to:

"**B. Comparison of Powder Mix Active-Uniformity Data With Dynamically Sampled In-Process Dosage-Unit Active-Uniformity Data**"

so that the title here is similar to the title in IV.B.

In addition, *because there is no text that addresses this subject*, this reviewer proposes that the following text be added after Line 298:

"Proceed as directed in Subsection IV.B to compare the findings for the blend data's sample uniformity statistics (sample and batch) to those of the in-process dosage-unit data's sample uniformity statistics (sample and batch). When the results found are as expected and predict that all dosage units will, if tested, conform to their expectations, make the appropriate specification updates and reports for the dosage units in the same manner as outlined in Subsection IV.B."

Similarly, to complete this Section, V., a Subsection "V.C." is needed.

To address, this reviewer suggests that the following text be added after the previous text:

"**C. Comparison of the Data From the Dynamically Sampled Representative In-process Samples To the Data From the Representative Finished Product Samples**

Proceed as directed in Subsection IV.C to compare the findings for the in-process dosage-unit data's sample uniformity statistics to those of the finished dosage-unit data's sample uniformity statistics. When the results found are as expected and predict that all the dosage units in the batch should, if tested, conform to their expectations, make the appropriate specification updates and reports for the dosage units in the same manner as outlined in Subsection IV.C."

Lines 298-311, "

~~**VI. VERIFICATION OF MANUFACTURING CRITERIA**~~

"~~You should complete the assessment of powder mix uniformity and correlation of stratified in-process dosage unit sampling development procedures before establishing the criteria and controls for routine manufacturing.~~ This section describes the sampling, testing, and evaluation of in-process dosage units collected using stratified sampling. These ~~exhibit and process validation~~*process conformance* batch data are used to support implementing the stratified sampling method described in this guidance. ~~We also recommend that you assess the normality and determine RSD from the results of stratified in-process dosage unit sampling and testing that were developed. The RSD value should be used to~~ The manufacturing process will be ~~classifyied the testing results as either *readily pass* *passing* (RSD ≤ 4.0%, *marginally pass* *passing* (RSD ≤ 6.0%) or *inappropriate* for demonstration of batch homogeneity (at least 1 batch has an RSD > 6.0%). The procedures are discussed in the following sections:~~"

Because the guidance provided does not address general uniformity and the stratified sampling proposed does not take *batch-representative samples* of either the final blend or, *as the term "stratified sampling" is defined*, the in-process dosage units, this reviewer cannot support the commenter's suggestions nor, for that matter, the original text.

Because **21 CFR 211.110** requires the monitoring of all variable factors that may be responsible for causing "variability in the characteristics of in-process material and the drug product," any general guidance on in-process uniformity must address all of the critical variable factors in a given formulation.

Upon reflection, this reviewer understands that the Agency should refrain from issuing any prescriptive language in this guidance because the nature, level and required degree of uniformity required to assure the requisite level of uniformity in the in-process materials and the drug product *varies from drug product to drug product*.

Based on the preceding, this reviewer recommends retaining this section but rewording it as follows:

"**VI. VERIFICATION OF MANUFACTURING CRITERIA**

As discussed in Section V, you should complete the assessment of the uniformity of: **a)** the final powder mix, **b)** the in-process dosage units and **c)** the finished drug-product dosage units as well as all comparisons involving the entities involved before establishing the criteria and controls for routine

manufacturing. *After you have established the specifications, acceptance criteria, and process controls for each stage*, you should continue to manufacture, *after the initial validation or conformance batches*, using the full set of acceptance criteria and process controls until the production history (typically, not less than ten [10] batches, though the number required depends on the exact findings) is sufficient to: **a)** implement process trending (e.g., control charting) **and b)** assess the validity of the existing specifications, acceptance criteria and process controls. IF that extended history confirms the validity of the specifications, acceptance criteria, and process controls, finds that all batches met the *acceptance criteria* for all critical variable factors and were released, and identifies and justifies a reduction in the *number of representative samples tested* that is predictive for a given monitored variable factor, THEN the firm should submit the proposed changes and the supporting information as suggested for a CBE-0 submission.

In addition, at each 'periodic review,' *or when there are any material improvements in the controls or significant improvements in the uniformity outcomes*, the manufacturers should review the entire historical data file and act when and as the data therein indicate. Based on that review, they should either confirm the validity of the existing manufacturing criteria (specifications, acceptance criteria, process controls) or use the information obtained to justify any change that reduces the number of *batch-representative samples* to be evaluated for a given variable factor.

In all cases, the manufacturers who wish to reduce their testing can use *scientifically sound* and *appropriate* staged evaluation plans with *acceptance criteria* that are established as being appropriate to each stage.

In addition, *for partially correlated variable factors* (such as active content and active availability, or active content and active impurity/degradant level) *which are evaluated by testing*, the manufacturer may be able to justify using a 'REDUCED' sampling plan for one of the correlated variable factors after sufficient batches are manufactured to establish a 'track record' of unbroken acceptability of the drug product batches."

Based on the reality that content uniformity is a necessary but not sufficient requirement for demonstrating CGMP-compliant in-process uniformity, **Lines 313-417** should be deleted from the draft guidance for all of the reasons cited previously concerning the need for batch uniformity to be assessed for *all* of the *critical* variable factors, not just active content, against the appropriate *scientifically sound specifications*.

In addition, some of what is stated here, such as extensive studies involving "significant event" points, properly belongs in the process development portion of the uniformity studies that must be conducted to meet the CGMP ***minimums*** for in-process materials and the in-process drug product.

Finally, as proposed, the criteria which follow are neither *scientifically sound* nor *appropriate* for the samples tested because the criteria are required to assure that the entire in-process *batch* is acceptably uniform – not that the samples tested just happen to meet the weak criteria proposed.

"**1A. In-Process Dosage Unit Sampling and Analysis**

We recommend the following steps:

- Carefully identify locations[20] throughout the compression or filling operation to sample in-process dosage units. The sampling locations should also include significant process events such as hopper changeover, filling or machine shutdown and the beginning and end of the compression or filling operation.[21] There should be at least 20 locations with 7 samples each for a minimum total of 140 samples. These include periodic sampling locations and significant event locations.
- Sample at least 7 in-process dosage units from each sampling location.
- Assay at least 3 of the 7 and weight correct each result. (The number of samples should be specified and justified for a given product and process.) Assay all 7 per location ifs required in Section V.A.
- Analyze the dosage units according to the flowchart in Attachment 1. Adequate Powder Mix is demonstrated, if for each batch:
  - RSD of all individuals is < 6.0%
  - Each location mean is within 90.0% - 110.0% of target potency
  - All individuals (not weight corrected are within 75% and 125 % of the target potency

[20] Prior identification of appropriate sampling locations is described in Section IV.B of this guidance.

[21] Thebeginning and end samples are taken from dosage units that would normally be included in the batch

- Conduct an analysis of the dosage unit stratified sampling data to demonstrate that the batch has a normal assess the active ingredient distribution of active ingredient throughout the batch (e.g., visual assessment of a histogram or a probability plot). Indications of trends, bimodal distributions, or other forms of a distribution other than normalbell-shaped should be investigatedevaluated. If these occurrences significantly affect your ability to ensure batch homogeneity, these should be corrected.
- Prepare a summary of this analysis. Potential investigation results along with a description of batch normalitydistribution should be included in the summary. Submit this summary with the application as described in section VIII of this guidance.

2. Classifying the Test Results

In addition to this analysis of batch normality Additionally, we recommend you classify the results as *readily pass* or *marginally pass* according to the following procedures:

B.Criteria to Meet *Readily Pass* Classification

For each separate batch, compare the weight corrected test results to the following criteria:

- For all individual results (for each batch n ≥ 60) the RSD ≤4.0 percent.
- Each location mean is within 90.0 percent to 110 percent of target strengthtarget potency.
- All individual results without weight correction are within the range of 75.0 percent to 125.0 percent of target strengthtarget potency.

If your test results meet these criteria for all batches, they are classified as *readily pass* and you can start routine batch testing using the Standard VerificationCriteria Method (SCVM) described in section VII. If your test results for any of the batches fail to meet these criteria, you may choose to test additional location samples and include these results to compare to *readily pass* criteria. Alternatively, we

~~recommend that you may compare the results to with the *marginally pass* criteria described below with or without additional test results~~.

~~C. Criteria to Meet the Marginally Pass Classification~~

~~If your dosage unit test results fail to meet the criteria for the *readily pass* classification, you should assay the remaining dosage units (all 7 units per location) and compare the weight corrected test results to the following criteria:~~

- ~~For all individual results (for each one batch n ≥ 60140) the RSD ≤ 6.0 percent.~~
- ~~Each location mean is within 90.0 percent to 110 percent of target strengthtarget potency.~~
- ~~All individual results without weight correction are within the range of 75.0 percent to 125.0 percent of target strengthtarget potency.~~

~~If your test results meet these criteria, results can be classified as *marginally pass*. If your samples do not meet these criteria, we recommend that you investigate the failure, find justified and assignable cause(s), correct the deficiencies, and if appropriate, repeat the powder mix homogeneity assessment, in-process dosage unit sampling correlationcomparison, and initial criteria establishment procedures. The disposition of batches that have failed the marginally pass criteria is outside of the scope of this guidance.~~

~~C. Establish the Relationship Between Stratified In-Process Samples and the Finished Product~~

~~In order to use in-process samples to fulfill the compendial uniformity of dosage units requirement for finished products, we recommend the following steps (this does not need repeated, if the comparison was performed during development):~~

> **Note:** Factually, there is **no** "compendial uniformity of dosage units requirement for finished products" ***prior to*** the ***release of*** the ***batch*** nor, *for that matter*, are the **USP**'s requirements applicable to other than the *post-release* "in commerce" *article*, as said *article* is defined by the **USP**.

- ~~Conduct testing for uniform content of the finished product using an appropriate procedure or as specified in the Abbreviated New Drug Application (ANDA) or the New Drug Application (NDA) for approved products.~~

> **Note:** Factually, the CGMP regulations at **21 CFR 211.165(d) clearly** require the use of "statistical quality control" to assess the finished product for release as follows:
>
> "Sec. 211.165 Testing and release for distribution.
>
> (d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels."
>
> Therefore, ***any*** procedure that fails to comply with **all** of the ***clear requirements*** of **21 CFR 211.165(d)** in a *scientifically sound* and *appropriate* manner does not comply with CGMP – including any non-complying procedure in ***any*** ANDA or NDA.

- ~~Compare the results of stratified in-process dosage unit analysis with uniform content of the finished dosage units from the previous step. This analysis should be done without weight correction.~~[22]

- ~~Prepare a summary of the data and analysis. If the stratified in-process data provides assurance of uniform content of the finished product, then the in-process data may be routinely used to demonstrate both uniformity of blend and final product. See section VII of this guidance for reporting requirements.~~

> **Note:** Factually, even if the procedures were to establish "content uniformity," without establishing the uniformity of the other components that are critical to the safety and efficacy of the dosage units (*which components the commenter's suggestions knowingly disregar*d) the procedures outlined in this guidance cannot validly be used establish the ***overall uniformity*** of:
>
> **A.** Any blend,
> **B.** The in-process dosage units, **or**
> **C.** The finished dosage units.

[22] ~~Weight correction is a mathematical correction to eliminate the effect of potentially variable tablet dosage unit weight on measurement f mix adequacy see Glossary, Section IX~~.

- ~~If the in-process samples cannot be used to assure uniformity of dosage units, then the compendial test on the final product will need to be continued in addition to the in-process stratified testing for blend uniformity.~~

> **Note:** Neither the "compendial test" for content uniformity nor the "compendial test" for any other test meet the **clear** requirements of **21 CFR 211.165(d)**.
>
> Since all of the **USP**'s "sample/test plans" are not based on statistical sampling plans (as clearly set forth in the **USP**'s ***General Notices***), no "compendial test" can meet **21 CFR 211.165(d)**'s **clear** "meet … appropriate statistical quality control criteria as a condition for their approval and release" requirement.
>
> This is the case because meeting such "appropriate statistical quality control criteria" clearly requires the use of statistically valid sampling plans.

~~D. Sample Locations for Routine Manufacturing~~

~~We recommend that you prepare a summary of the data analysis from the powder mix assessment and stratified sample testing. From the data analysis, you should establish the stratified sample locations for routine manufacturing, taking into account significant process events and their effect on in-process dosage unit and finished dosage unit quality attributes. You should identify at least 10 sampling locations (or more) during capsule filling or tablet compression to represent the entire routine manufacturing batch.~~"

Lines 419-525 should be deleted from the draft guidance for all of the reasons cited previously concerning the need for batch uniformity to be assessed for *all*

of the *critical* variable factors, not just active content, against the appropriate *scientifically sound* specifications.

21 CFR 211.110 requires the monitoring of **all** variable factors that may be responsible for causing "variability in the characteristics of in-process material and the drug product."

Therefore, any general guidance on in-process uniformity must address all of the critical variable factors in a given formulation.

Because the guidance provided does not address *general uniformity* and the "stratified" sampling proposed does not ensure that *batch-representative* samples of either the final blend or, as the term "stratified sampling" is defined, the in-process dosage units that are taken and tested, this reviewer cannot support the commenter's suggestions nor, for that matter, the original text.

Upon reflection, this reviewer clearly understands that the Agency should refrain from issuing any prescriptive language in this guidance because the nature, level and required degree of uniformity required to assure the requisite level of uniformity in the in-process materials and the drug product *varies from drug product to drug product*.

Based on the preceding realities, this reviewer recommends replacing **Lines 419-525** with the with the following text:

"**VII. ROUTINE MANUFACTURING BATCH TESTING ~~METHODS~~ PROCEDURES**

You should use the outcomes observed in Section VI and the hierarchical sample testing procedures and switching rules (derived from those in the appropriate consensus standards for *batch-representative* dosage units and those developed using the appropriate valid statistical procedures found in text treating the general uniformity of non-discrete materials for the *batch-representative samples* from blends) to control the testing procedures used for each batch.

You should use the *specifications, sample and batch acceptance criteria,* and *other process controls* that comply with all the applicable strictures of **21 CFR 211.110** and **21 CFR 211.165** to control, monitor and validate each *significant phase* (or stage) in the manufacture of *each batch*.

In addition, at each "periodic review," *or when there are any material improvements in the controls or significant improvements in the uniformity outcomes*, the manufacturers should review the entire historical data file, and act when and as the data therein indicate. Based on that review, they should either confirm the validity of the existing manufacturing criteria (specifications, sample and batch acceptance criteria, and other process controls) or use the information obtained to justify any change that reduces the number of batch-representative samples to be evaluated for a given variable factor.

In all cases, the manufacturers who wish to reduce their testing can use *scientifically sound* and *appropriate* hierarchical (staged) evaluation plans with *batch acceptance criteria* that are established as being appropriate to each phase of manufacture.

In addition, *for partially correlated variable factors (such as active content and active availability, or active content and active impurity/degradant level) which are evaluated by testing*, the manufacturer should use their justified "reduced sampling plans" for each of the correlated variable factors that, as the manufacturer established in **Section VI**, provide a *scientifically sound* and *appropriate* confidence level and risk that is not significantly greater than the risk for the "normal sampling plan" as the starting point for the assessment of the uniformity of the output of each phase (or stage) of manufacturing."

~~"We recommend that you evaluate the routine manufacturing batches using in-process stratified samples against the following criteria, after completing the procedures described above to assess the adequacy of the powder mix and uniform content of the finished dosage form.~~

~~These routine batch-testing methods include the Standard Criteria Method (SCM) and the Marginal Criteria Method (MCM). The SCM consists of two stages, each with the same *accept/reject* criteria. The second of the two stages recommends using a larger sample size to meet these criteria. The MCM uses *accept/reject* criteria that are different from the SCM.~~

~~If the batch data fail to conform to the SCM criteria, we recommend continued sampling and testing to intensified criteria (MCM). Both verification methods and the procedures for switching from one to the other are detailed below and in the flow chart in Attachment 2.~~

~~A. Standard Criteria Method (SCM)~~

~~We recommend using the SCM verification method when either~~any of the following conditions ~~are~~is ~~met:~~

- ~~Results of establishing initial criteria are classified as *readily pass* and no previous batch failed the SCM criteria.;~~
- ~~Previous routine batch was appropriately evaluated using SCM and SCM criteria.~~
- ~~Results of testing the previous routine batches using to the MCM pass the criteria for switching to the SCM (see section C below).~~

~~The SCM should meet the same criteria using a different number of sample test results as described below:~~

~~*1. Stage 1 Test*~~

~~To perform the stage 1 test, we recommend that you (1) collect at least 3 dosage units from each sampling location, (2) assay 1 dosage unit from each location, (3) weight correct the results, and (4) compare the results with the following criteria:~~

- ~~RSD of all individual results ($n \geq 10$) $\leq$ 5.0 percent.~~
- ~~Mean of all results is 90.0 percent to 110.0 percent of target assay.~~

~~If your results pass these criteria, the adequacy of mix for the batch is adequate and you can use stage 1 of SCM for the next batch. If the results pass these criteria and the adequacy of mix and uniformity of dosage unit content for the batch are adequate, you can use the SCM for the next batch. If test results fail stage 1 criteria, you should conduct extended testing to stage 2 acceptance criteria.~~

~~*2. Stage 2 Test*~~

~~To perform the stage 2 test, we recommend that you assay and weight correct the remaining two dosage units (from stage 1) for each sampling location. And Ccompute the mean and RSD of data combined from both stage 1 and stage 2. Compare the results with the following criteria:~~

- ~~For all individual results (n ≥ 30) the RSD ≤ 5.0 percent.~~
- ~~Mean of all results is 90.0 percent to 110.0 percent of target assay.~~

~~If your results pass these criteria, the adequacy of mix and uniformity of content for the batch areis adequate and you can use stage 1 of SCM for the next batch. If test results fail the criteria, use the MCM described in the next section.~~

~~B. Marginal Criteria Method (MCM)~~

~~We recommend using the MCMAfter powder mix assessment, in-process dosage unit stratified sampling correlation and initial criteria establishment, we recommend that you use the MCM when anyeither of the following conditions areis met:~~

- ~~Results of initial criteria establishment qualified as *marginally pass*.~~
- ~~Previous routine batch was appropriately evaluated using MCM and met MCM criteria.~~
- ~~Results of initial criteria establishment qualified as *readily pass* or a~~ The current routine batch ~~was tested according to SCM and the test results failed both stage 1 and stage 2 criteria.~~
- ~~Previous batch was first tested using SCM, but had to switch to MCM to pass.~~

~~To perform the MCM test, we recommend that you (1) have assayed all 3 dosage units from each sample location, (2) weight correct the results, and (3) compare the results with the following criteriaThen, we recommend you use~~ (note: ~~the weight-corrected results from the stage 2 SCM analysis and~~ are ~~compared~~ to ~~this with the MV~~CM criteria ~~if stage 2 SCM does not pass)~~:

- ~~For all individual results (n ≥ 30) the RSD ≤ 6.0 percent.~~
- ~~Mean of all results is 90.0 percent to 110.0 percent of target assay.~~

~~We recommend that all results from analysis of any remaining location samples be computed with the stage 2 SCM data. No test results should be removed from the analysis. If the test results pass these criteria, the adequacy of mix and uniformity of content for the batch are~~ is adequate.~~:~~ ~~And w~~We ~~recommend that you continue to test routine manufacturing batches with MCM criteria. If the test results fail the criteria, you should no longer use the verificationRoutine Manufacturing Batch T~~testing ~~M~~methods ~~(Section VI)~~ ~~to ensure adequacy of mixing or uniformity of content until you investigate the failure (per 21 CFR 211.192). That is, to establish justified assignable cause(s), take necessary corrective actions, and if appropriate,repeat the powder mix assessment, stratified sample correlation~~comparison~~, and initial criteria establishment procedures. Or, adopt at, in, or on-line measurement systems to ensure adequate powder mix assessment.~~"

~~C. Switching to Standard Test~~ Criteria Method from Marginal Test Criteria Method

~~It is appropriate to switch to the SCM when the following criterion is met:~~

- ~~Five consecutive batches pass the MCM criteria and result in~~for each batch the ~~RSD ≤ 5.0 percent~~"

This reviewer recommends the following replacement text for **Lines 528-571:**

TITLE (Line 528):

"VIII. REPORTING THE USE OF ~~STRATIFIED~~ *BATCH- REPRESENTATIVE IN-PROCESS DYNAMIC AND STATIC* SAMPLING AND EVALUATION PLANS "

Considering the text, this reviewer offers the following the changes to **Lines 530 through 571**:

"A. ~~Applications~~ *Submissions For Drug Products That Are* Not Yet Approved *Or Licensed*

This section refers to the scientific data analysis and other information that should be submitted ~~to an NDA or ANDA~~ *in the appropriate portions of the Chemistry, Manufacturing, and Controls section of any submission (ANDA, NDA, AADA, NADA) of a drug product for approval or licensing.* ~~Information~~ *The information* submitted in the ~~application~~ *submission* should include *the intermediate data and result values, investigations, justifications, rationales,* summary reports and scientific analyses or statements about the method being used. The *truly* raw data collected *for all the samples evaluated* and *the supporting standards' raw data* to support using this method should be maintained at the manufacturing site.

We recommend that, ~~when~~to the extent that such is available[23], you provide the following information in the Manufacturing Process and Process Controls section of the application (CTD[24] 3.2.P.3.3).

[23] Sufficient data may not be available from full-scale batches at the time of the initial submission. If data summaries are not included in the application, they should be included in validation or development documents maintained at the site. Preliminary data at small-scale may be submitted, but the final analyses and comparisons should be performed on data from full-scale batches.

[24] *M4Q: The CTD – Quality*, one in a series of guidances that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the FDA.

- Statement that the methods in this guidance are *only* being used *and can only be* to demonstrate the ~~adequacy~~ *uniformity* of *the final* powder mix, *the freshly formed dosage units, and the "finished, unpackaged" drug product units* or a description of *the* alternative methods that *the manufacturer has used to* demonstrate the ~~adequacy~~ *uniformity* of the powder mix*, the in-process formed dosage units, and the in-process finished dosage forms with respect to the active content and the other key variable factors (e.g., disintegrants, release retardants, stabilizers, and lubricants) that are clearly required to be adequately controlled under **21 CFR 211.110***. ~~Method that will be used to demonstrate the adequacy of powder mix.~~
- Summary of *the* data *and data* analysis from the powder mix assessment ~~and~~ as well as from ~~stratified~~ ~~sample testing~~ *the dynamic and static batch-representative sampling, examination, testing, and evaluation of the in-process "freshly formed" dosage units or the "finished' dosage units to demonstrates compliance with **21 CFR 211.110**, and for the finished drug product, the statistical quality control requirements of **21 CFR 211.165(d)***

with respect to the active content, and any other variable factor(such as Dissolution, Drug Release, impurity, water content, residual solvents) that may adversely impact the safety and efficacy of the dosages units in the batch.

- ~~Summary of the stratified~~ *An informative tabulation of the valid results obtained from the* in-process *batch-representative* dosage ~~unit~~ *units dynamically or statically sampled and tested to support the uniformity of the of the drug product batches with respect to the active and an analysis of that data that demonstrates:* ~~sampling data analysis demonstrating a normalevaluating the~~
  a) *the degree to which the data approximate a* normal distribution of active ingredient *and the other components that govern the availability of the active* in the batch,
  b) the validity of the batch release specifications set for the in-process final blend, the "freshly formed" dosage units and the "finished" drug product,
  c) the compliance of the sampling and testing of the output of the various in-process manufacturing steps and the finished drug product with the CGMP requirements, and
  d) the validity of the controls on the incoming components, in-process materials and the drug product.
- Summary of the powder mix*, in-process formed dosage units, and drug product* sampling data *and a supporting scientifically sound and appropriate batch-statistics-based* analysis demonstrating that ~~it~~ *each* met the minimum *CGMP-compliant in-process statistics-based* criteria for *the initial process* validation and *for* establishing *the validity of the* initial criteria *used to establish the uniformity of the various materials with respect to the active content as well as the other variables that can adversely impact the safety and efficacy of the drug product batch.*

We recommend that you provide the following information in the Drug Product Specification section of ~~the application~~ *any submission* (CTD 3.2.P.4.1)~~, if~~ when applicable:

- ~~Statement~~ *A declaration* in the *drug* product specification stating that the methods in this guidance are being used to demonstrate finished product uniformity of content *for each active or other critical variable factor,* or a description of *the scientifically sound and appropriate batch-statistics-based CGMP-compliant* alternative methods used to demonstrate finished product uniformity of content *for each active and other critical factor*

We also recommend that you provide the following information in the Pharmaceutical Development Information section of the application (CTD 3.2.P.2.2):

- Summary of *the results'* data *and the scientifically sound* analysis ~~for~~ *thereof that establishes the* ~~correlation~~comparison ~~of~~ *relationship between the batch-representative* in-process dosage unit *uniformity results for each active* ~~stratified sampling with~~ *and the batch-representative* finished product uniformity of content *results for each active ingredient as well as the corresponding relationships for each other critical variable factor identified for the blend or the finished drug product units.*

- Summary of *the results'* data *and the scientifically sound* analysis ~~for~~ *thereof that establishes the degree of* ~~correlation~~ comparison ~~of~~ *relationship between the batch-representatively-sampled* powder mix uniformity *results for each active ingredient* ~~with~~ *and the batch-representative* in-process dosage unit ~~stratified sampling~~ *results for each active ingredient as well as the corresponding relationships for each other critical variable factor identified for the blend or the dosage units.*

B. Postapproval Change

If you plan on changing *any of* ~~the~~ *your* existing controls for ~~adequacy~~ *the active-content uniformity* of mix and*/or* the uniformity of content *for each active in the in-process dosage units and/or the drug product*, or those of any other critical variable factor, to the methods described in this guidance, the change should be considered ~~a minor change as described~~ *according to the criteria set forth* in the *Agency's guidance* ~~postapproval changes guidance.~~ *for postapproval changes.*[25] ~~We~~ *When the change can properly be classified as a minor change, we* recommend you provide a notice of the change in the next annual report along with the information indicated in section A, above. ~~The~~ *While the intermediate results, standards, and statistically derived data should be tabulated and submitted, the* raw data collected to support changes can be maintained at the manufacturing site.

[25] FDA's guidance for industry on *Changes to an Approved NDA or ANDA*."

For Lines 573-608, **Glossary**, this reviewer recommends the following text:

"**GLOSSARY**

Absolute, as used to define the *limits for a variable, means the maximum bounded range for that variable. For example, an* ~~acceptable~~ *absolute content* range ~~(+/- 10%) in~~ *is a content range which is independent of the value of the mean value observed for any set of samples and within* which ***all*** individual sample values must fall ~~and which is independent of the value of the mean~~. *For example, if ~~the mean of all blend samples is 95.0%,~~ the manufacturer's established requirement is that all blend samples must fall within 95.0 % to 105 % of the target value, the* ***absolute*** *range is ~~85.0% to105.0%, not (95.0% +/- 9.5%)~~ 95.0 % to 105 % and not a) 100 +/- 5 % or b), when the sample tested ranges from 96.0 % to 105 % and the mean is 99.5 %, 99.5 % - 3.5%/+5.5 %).*

Exhibit Batches refer to any batch submitted in support of an ~~NDA or ANDA~~ ANDA, NDA, ANADA, NADA, DMF, or VMF. This includes bioequivalence, ~~test~~ *development, start-up, initial validation*, and commercial production batches of a drug product.

In-process dosage unit is a capsule or tablet as it exists during or at the completion of any in-process step starting from the time the dosage unit is formed in the manufacturing process ~~before it is coated or~~ and continuing until it is packaged. *For example,* in a process that has processing steps (phases, stages) that: a) forms the final blend into tablet cores, b) film-coats the cores with a color, c) overcoats the color coat with a clear coat, d) prints identification on the clear coated units, e) waxes and polishes the printed units, f) holds the polished units in bulk until the batch is released for packaging, and g) packages the released polished units for distribution, the outputs of steps "a)" through "e)" are **all** collections of in-process dosage units. In the example, the corresponding appropriate "in-process dosage unit" phase-differentiating

identifiers could be: a) "freshly formed," b) "color coated," c) "clear coated," d) "printed," and e) "polished."

RSD is the accepted acronym for what is commonly called the~~,~~ relative standard deviation; *RSD = [(standard deviation)/(mean)] x 100%. Usually,* RSD is the overall "relative standard deviation of the results from the sample tested."

Significant event is any operation during solid dosage production process that can ***adversely*** affect the integrity of the in-process materials and, hence, their quality attributes. Transferring powder from a blender to a bin or from the bin to a hopper are two examples of significant events in ~~the~~***a*** blending ~~and~~ ***or*** compression process ***step***.

Stratified sampling is the process of collecting a representative sample by selecting units deliberately from various identified locations within a lot or batch, or from various phases or periods of a process ~~to obtain a~~ Stratified sampling of ~~sample~~ dosage unit ~~that~~ specifically targets locations throughout the compression/filling operation that have a higher risk of producing failing results in the finished product uniformity of content; then, random dosage units are selected within these identified locations.. ***Stratified sampling*** **is,** *therefore, by definition,* **a non-CGMP-compliant form of sampling** *because the drug product CGMP regulations require the samples to be "representative"* (as that term is defined in **21 CFR 210.3(b)(21)**) *of the batch* (as required by **21 CFR 211.160(b)(2)**) – not from a *non-batch-representative* set of locations that are thought to have a 'higher risk of producing failing results.' **Stratified sampling** does not provide samples that meet this CGMP **minimum** which would require the samplings to be from locations or time points that are representative of the batch. Moreover, to be ***batch-representative****, periodic samples* taken during a production step must: **a)** span the step **and b)** be *representative* of the local variability in the production step at the time of the sampling.

Target assay/Target Potency is the intended strength or intended amount of active ingredient in the dosage unit.

~~**Validation**~~ **Process conformance batch** is a batch manufactured and tested to verify the proposed routine manufacturing process controls are adequate. Because the in-process controls (**21 CFR 211.110(a)**) **require** the manufacturer to have, and follow for each batch, established control procedures "to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product," each production batch is a required to be a batch that validates the process.

Weight correct is a mathematical correction to ~~eliminate the effect of potentially variable tablet weight on measurement of mix adequacy~~ validly normalize the content result obtained for the level of active in a "freshly formed" dosage unit to what that active content result would probably have been had that dosage unit been formed at the manufacturer's established target weight. *For example, a tablet with a measured strength of 19.4 mg and weight of 98 mg has a weight fraction active content of 0.197959184* mg_{Active}/mg_{Tablet} (mg_{Active}/mg_{Tablet} *= 19.4 ÷ 98 = 0.197959184 ~~mg/mg~~). ~~Label~~ If the drug-product's label claim is 20 mg per each 100 mg tablet, ~~so~~ the weight—corrected result percent of active in the dosage unit tested is ~~0.198~~0.197959184* $\frac{~~mg_{Active}~~}{~~mg_{Tablet}~~}$ *÷ 0.20* $\frac{~~mg_{Active}~~}{~~mg_{Tablet}~~}$ ** 100 ~~%~~ = 98.9795918 % of the label claim. Rounding that result to two decimal places and using the result to estimate the content of active in the blend that went into that tablet, you find that the blend content was probably ~~or~~ 99% of ~~target~~ the blend ~~assay~~ target content level for the active.*

Moreover, in lieu of the preceding changes, this reviewer suggests that it would be better to replace the draft's Glossary with the following **GLOSSARY**:

"GLOSSARY

A. TERMS DEFINED BY REGULATION

1.	***"Acceptance criteria"***	**21 CFR 210.3(b)(20)**
2.	***"Active ingredient"***	**§§ 210.3(b)(7)**
3.	***"Batch"***	**§§ 210.3(b)(2)**
4.	***"Component"***	**§§ 210.3(b)(3)**
5.	***"Drug product"***	**§§§ (b)(4)**
6.	***"Inactive ingredient"***	**§§§ (b)(8)**
7.	***"In-process material"***	**§§§ (b)(9)**
8.	***"Lot"***	**§§§ (b)(10)**
9.	***"Manufacture, processing, packing, or holding of a drug product"***	**§§§ (b)(12)**
10.	***"Quality control unit"***	**§§§ (b)(15)**
11.	***"Raw data"***	**21 CFR 58.3(k)**
12.	***"Representative sample"***	**21 CFR 210.3(b)(21)**
13.	***"Strength"***	**§§ 210.3(b)(16)**

B. TERMS OR PHRASES DEFINED BY STATUTE

1.	***"Abbreviated drug application"***	**21 U.S.C. 321 (aa)**
2.	***"Adulterated drug"***	
	(contaminated with filth)	**21 U.S.C. 321 (a)(1)**
	(made under filthy conditions)	**(a)(2)(A)**
	(CGMP non-compliant)	**(a)(2)(B)**
	(in a contaminated container)	**(a)(3)**
	(contains "unsafe" color)	**(a)(4)**
	(contains "unsafe" animal drug)	**(a)(5)**
	(feed containing "unsafe" animal drug)	**(a)(6)**
	(strength, quality, or purity differs from official compendium)	**(b)**
	(misrepresented strength, quality, or purity	**(c)**
	(mixed with or substituted with another substance)	**(d)**
3.	***"Counterfeit drugs"***	**21 U.S.C. 321 (g)(2)**
4.	***"Current good manufacturing practice (CGMP)"***	**21 U.S.C. 351 (a)(2)(B)**

"A drug … shall be deemed to be adulterated —if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with ***current good manufacturing practice*** to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; …"

5.	***"Drug"***	**21 U.S.C. 321 (g)(1)**
6.	***"Drug Product"***	**21 U.S.C. 321 (dd)**
7.	***"New animal drug"***	**21 U.S.C. 321 (v)**
8.	***"New drug"***	**21 U.S.C. 321 (p)**
9.	***"Official compendium"***	**21 U.S.C. 321 (j)**

10. "Safe" **21 U.S.C. 321 (u)**

C. TERMS OR PHRASES DEFINED FOR USE IN THIS GUIDANCE

Absolute Range, as used to define the limits for a variable, *means* the bounded range for that variable. For example, an absolute content range is a content range: a) which is independent of the value of the mean value observed for any set of samples and b) within which all individual sample values are expected to fall. IF: **a)** the manufacturer's established requirement is that all blend samples must fall within 95.0 % to 105 % of the target value, THEN the blend ***sample's*** **absolute acceptance range** is 95.0 % to 105 % and not 100 +/- 5 % **or b)**, when the sample tested ranges from 96.0 % to 105 % and the mean is 99.5 %, the sample's **absolute result's range** is from 96 % to 105 % – *not the apparent dispersion about the observed mean (99.5 % -3.5%/+5.5 %).*

Attribute, as used in the sciences, including statistics, *means* a quality of something and, accordingly assessments of an attribute are qualitative in nature; antonym: variable

Characteristic *means* any qualitative (attribute) or quantitative (variable) defining feature.

Confidence *means* how certain one can be about the validity of the predicted characteristics of a **population**. **Confidence** depends on the valid application of a given statistical procedure to a sufficient set of observations made on a **population-representative sample**. In general, the larger the number of population-representative units tested the higher the level of confidence that the values observed for the units tested can be used to accurately predict the true population distribution of unit values.

Confidence interval *means* the predicted range of values or states obtained from applying a *scientifically sound* and *appropriate* statistical estimation procedure to the results obtained from a **population-representative** set of observations made on a **sample**.

Conformance batch (sometimes referred to as a "validation" batch or "demonstration" batch) *refers to* any batch prepared to demonstrate that, under normal conditions and defined ranges of operating parameters, the commercial scale process appears to make acceptable product. [**Note:** Prior to the manufacture of a conformance batch, the manufacturer should have identified and controlled all critical sources of variability.]

Correlation, as used in statistics, *means* the degree to which two or more variables are related and change together. ***"Correlation coefficient"*** *means* a number or function (having a value of between –1 and +1) that indicates the probable degree of correlation between two variables.

Critical, as that term applies to pharmaceutical products and processes**,** *is* an adjective that applies to any process or product *characteristic* that is *required to be controlled in a manner that complies with, or pertaining to any applicable requirement defined in, the drug CGMP as set forth in* ***21 CFR 210*** *through* ***21 CFR 226***. ***Non-critical****, in the same context,* is an adjective that applies to any process or product *characteristic that is above* or *in addition to* the ***minimums*** established in the drug CGMP – for example, the uniformity of the color of the finished tablets.

Distribution *is* a value ordered frequency table or figure depicting the range of values in the **population** and the number of entities having each value.

Dynamic sampling *means* the controlled removal of portions of a **population** while the **population** is being produced. When **dynamic**, **time-point sampling** occurs in pharmaceutical manufacturing during the production of a *batch* of drug product, the **sample** taken at each **sampling point** must, itself, be ***representative*** of the possible *variability* in the drug product at that point (**see Example 1**). As a consequence of this, each **dynamic sample** must encompass the *variability* at the point that said **sample** is being taken.

Example 1: Dynamic Sampling During Tablet Manufacture

Since a firm's sampling plan is dynamic and specifies taking *samples* from a hypothetical 21-station tablet press periodically, then the **sample** taken at each **sampling**

point must be some whole-number multiple of the 21 tablets produced at that **point**. Thus, when the **sampling plan** for this 21-station press requires sampling at start up, "**n**" time points during tablet production, and at the end of production, the final *sample* should consist of at least (**[n + 2] x 21 x *some integer multiple***) tablets.

Evaluate *means* to consider or examine something in order to judge its value, quality, importance, or condition.

Examine, *means* to observe something in some detail (e.g., *the drums were opened and their contents examined for the presence of foreign particulate matter)*.

Exhibit batch (or exhibit lot) *refers to* any ***batch*** (or ***lot)*** submitted in support of an ANDA, NDA, ANADA, NADA, DMF, or VMF. This includes any submitted bioequivalence, development, start-up, initial validation, and commercial production ***batch*** (or ***lot***) of a drug product.

Factor *means* something that contributes to or has an influence on the result of something.

Grab sampling *means* **sampling** by choosing any convenient **sample** of some defined or minimum size (number or amount) from a **population**. The defined **USP sample**, the ***article***, *is*, of necessity, a **grab sample** as is, of necessity, any "in commerce" sampling from a small portion of a batch.

Initial validation, initial process conformance, performance qualification (PQ), or evaluation qualification (EQ) batch or **lot** *is* a **batch** or **lot** manufactured and tested to verify the proposed routine manufacturing process controls are adequate. Because the in-process controls (**21 CFR 211.110(a)**) **require** the manufacturer to have, and follow for each batch, established control procedures "to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product," each production batch (or lot) is required to be a one that validates the process – *thus* ***each routine production*** **batch** (or **lot**) *is* an ***ongoing*** **validation** *(or* ***Maintenance Qualification [MQ])*** **batch** (or **lot**).

In-process dosage unit *is* a capsule or tablet as it exists at the completion of any in-process step starting from the time the dosage unit is formed in the manufacturing process and continuing until it is ready to be packaged. For example, in a process that has processing steps (phases, stages) that:: **a)** forms the final blend into tablet cores, **b)** film-coats the cores with a color, **c)** overcoats the color coat with a clear coat, d) prints identification on the clear coated units, **e)** waxes and polishes the printed units, **f)** holds the polished units in bulk until the batch is released for packaging, and **g)** packages the released polished units for distribution, the **outputs of** steps "**a)**" **through** "**e)**" are **all** collections of **in-process dosage units**. In the example, the corresponding appropriate "in-process dosage unit" phase-differentiating identifiers could be: **a)** "freshly formed," **b)** "color coated," **c)** "clear coated," **d)** "printed," **and e)** "polished." *At the end of* ***Step "f,"*** the dosage units are **finished dosage units**. At the end of **Step** "**g**," the dosage units are the **finished packaged dosage units** (from which the *batch-representative samples* are required to be taken [**21 CFR 211.160(b)(2)**]) .

Inspection *is* the **sampling** of a **sample** from a **population** coupled with examining or testing that **sample**, or a *subsample* thereof, for compliance with predetermined **specifications**.

Measure *means* to find out the size, length, quantity, or rate of something using a suitable instrument or device, or to assess the quality of something by quantitatively comparing it to some standard.

The **normal, or Gaussian, distribution** *is* a unimodal symmetrical **distribution** having a **population** *mean*, **μ**, and **population** *standard deviation*, **σ**. The *variance* of this **distribution** is $\boldsymbol{\sigma^2}$. Its *mean* or average value**, μ**, is also its *mode* (the most frequent value) and *median* (the value that divides the distribution in half). This is the case because a **normal distribution** is both *unimodal* and *symmetrical*. Moreover, **σ** is the distance from the mean, **μ**, to the two inflection points on the curve that encompasses the **population** values. Thus, **μ** is the location parameter for a normal distribution and **σ** describes the spread, scatter or dispersion of the **population** about the *mean*. Defining ***z*** as the distance from the mean in units of standard deviation, the values of ***z*** can be computed using the formula:

$$z = (X - \mu)/\sigma \qquad (1)$$

Where **X** is a given value in the **population**.

Using z, we can ascertain the proportion, **P**, of entities in the **population** that have values smaller than any given z. The proportions found are such that 34.13 % of the **population** is between 0 and 1 or 0 and –1 z, 13.59 % between 1 and 2 or –1 and –2 z, 2.14 % is between 2 and 3 or –2 and –3 z and 0.14 % is outside of 3 or –3 z. Based on this, 68.26 % of the **population** is between –1 and +1 z, 95.44% is between –2 and +2 z, and 99.72% is between –3 and +3 z.

Population *means* any finite or infinite collection of individual entities. For control purposes, a **population** is also a collection governed by some property that differentiates between things that do and things that do not belong. The term **population** carries with it the connotation of completeness. Depending upon the setting, the drug-product CGMP regulations treat a *lot*, a *batch*, a small group of *batches*, or all of the *lots* or *batches* produced in a given time interval as the **population** being evaluated. *Lot* or *batch* quality evaluations must be designed to predict whether, or not, the *samples* tested (or examined) from a *lot* or *batch* being inspected not only meet their **specifications** but also **predict that** the ***lot*** or ***batch*** does, or does not, belong to the universe of releasable drug product.

Purity *means* the absence, or degree of absence, of anything of a different type – *tests to establish the purity of the water in the holding tank*.

Quality *means* an essential identifying property of something.

Representative Sample *means* any subset of a **population** whose measured characteristics can validly be used to predict the characteristics of the **population**. When a **CGMP** regulation requires a **representative sample**, that sample must be *representative* of the *lot* or *batch* addressed by said regulation. For a **sample** to be **representative**, it must satisfy three criteria:

1. It must be from all portions of the **population** or, *when sampling is performed during the production of the batch or lot*, it must appropriately *span* the production operation that it covers from start to finish.
2. Its *size* (*number*) must be large enough that the results obtained from testing or evaluating that number of entities or amounts can validly predict the **population's** distribution with respect to the parameter or parameters evaluated.
3. Each removal of entities or an amount in the set of removals that define the complete **sample** must be done so that its removal does not bias or affect the selection of the next removal in the set.

Representative inspection is the **sampling** of a **representative sample** from a **population** coupled with *examining* or *evaluating* (*testing*) that **representative sample**, or a **representative** *subsample* thereof, for compliance with predetermined *specifications*.

Representative sampling *means* **sampling** in a manner that is designed to assure that the **sample** taken is *representative* of the **population** from which it is taken. In order to make valid *nontrivial* generalizations about the **population** from the results obtained by evaluating a **sample** from said **population**, the **sample** must have been obtained by a **sampling** scheme that ensures four (4) conditions:

1. The **sample** set must *span* the population – be from all parts of the *batch* or, in the dynamic case, cover the production period from "start" to "end."
2. Relevant characteristics of the **population** sampled must bear an established or proven relation to the corresponding characteristics of the **population** of all possible **samples** associated with the sampling scheme used. [**Note:** In dynamic sampling, the number of **samplings** must be sufficient to reflect the variability in the production step that is being sampled, and each **sampling** must be ***representative*** of the local variability present at the time of **sampling**.]
3. The **population sample** must be of sufficient *size* that valid generalizations about properties of the **population** may be inferred from the results obtained from the evaluation of those properties

in the **samples**. The inferences from the results must be made using a recognized, proven "book of rules" whose validity rests on statistics, the mathematical theory of probability.

4. The sampling of any given **sample** in the **sampling** set that defines the complete **sample** must be done in a manner that ensures it does not bias the next **sample**.

RSD *is* the accepted acronym for what is commonly called the relative standard deviation; *RSD = [(standard deviation)/(mean)] x 100%. Usually,* in the pharmaceutical industry, RSD *is* the overall "relative standard deviation of the results from the sample tested."

Sample *means* any portion of a *population*. A **sample** is any subset of the **population**. It can be a single entity, a group of entities, or a portion removed from another **sample**. It carries the connotation of *incompleteness*.

Sample mean *is* the average of the measured values for the **samples** evaluated. Usually, the mean is computed using the formula:

$$\overline{X} = {}^{1}/_{n}\, \Sigma^{n}_{i=1} X_i \qquad (2)$$

Where the X_i are the values observed for the ***n* samples** evaluated.

Sample variance or, more accurately, the **sample estimate of variance**, denoted as s^2, *is* the estimate of the variance, the second moment about the **population** *mean*, μ. Usually, this statistic is computed using the formula:

$$s^2 = [n \Sigma^{n}_{i=1} X^2_i - (\Sigma^{n}_{i=1} X_i)^2] / [n\,(n\text{-}1)] \qquad (3)$$

However, the general formula that should be used is:

$$s^2 = [n \Sigma^{n}_{i=1} X^2_i - (\Sigma^{n}_{i=1} X_i)^2] / [n\,(n\text{-}f)] \qquad (3a)$$

Where ***f*** is the degrees of freedom consumed in the computation process.
When the X_is are "direct" measurements, then **f** is **1** because one degree of freedom is consumed in the computation of the "differences."
However, when the X_is are ratio measurements, as is often the case in hyphenated chromatographic/detector measurements using an Internal Standard, then **f** is **2** and the proper formula to use is:

$$s^2 = [n \Sigma^{n}_{i=1} X^2_i - (\Sigma^{n}_{i=1} X_i)^2] / [n\,(n\text{-}2)] \qquad (3b)$$

Sample variability or, more accurately, the **sample estimate of variability**, denoted as **s**, *is* the square root of the **sample estimate of variance**. This term is often referred to as the "*sample standard deviation*." That name is the source of the alternate abbreviation, "SD." While **variances** are additive, **variabilities** or *standard deviations* are not additive. Thus, if one needs to add or average *standard deviations*, one must first convert them into **variances** by squaring them. Then, the **variances** can be added and the square root of the sum is the *total standard deviation* or, *for like **variances***, dividing the sum by the number of like **variances** added gives the ***average variance***, and the square root of that **variance** is the *average standard deviation*.

Sample size has more than one meaning.

- For discrete **populations** (tablets, capsules, syringes, *etc.*), it is the number of entities (units) from a **population** that are either:
  - Removed by sampling or
  - Inspected (examined or tested) by some procedure or method.
- For *non-discrete* **populations** (blender loads, drums of a component, bulk liquids, *etc.*) it is the amount of material (by weight or volume) from a **population** that is either:
  - Removed by **sampling**, or
  - Inspected (examined or tested [evaluated]) by some procedure or method.

In the **USP**'s view, **sample size** refers to the minimum number of entities (the **USP *article***) for discrete populations. For non-discrete materials, the **USP *article*** (**sample size**) is the stated amount of material that is required for a given **USP** test or evaluation.

Depending on the context, the **FDA** and the Court (Judge Wolin in **USA v. Barr**) have used the term **sample size** to connote either:

- The physical amount of a non-discrete or discrete material that is to be *sampled* (a defined number of units in the discrete case or, in the non-discrete materials' case, nominally, at least three times the dosage unit weight) or
- The amount (number, weight, or volume) to be used in a given test or evaluation to generate a result.

Sampling *means* the controlled removal of any portion of a **population** for retention and/or examination or testing purposes.

Sampling plan *means* the *scientifically sound* and *appropriate* strategy used to take a valid **sample**.

Significant event *is* any event during solid dosage production process that can adversely affect the integrity of the in-process materials and, hence, their quality attributes. Transferring powder from a blender to a bin and from the bin to a hopper are two examples of significant events in *a* blending *or* dosage-forming process *step*.

Simple (unrestricted) **random sampling** *means* **sampling** in a manner that each entity in the **population** has an equal chance of being the first member of the **sample**; each remaining entity has an equal chance of being the second member of the **sample**; and so on – subject to the constraint that "each possible **sample** has an equal chance of being selected."

Specification *means* a detailed description of a component, material, intermediate, product, or control in terms of the numerical limits, ranges or acceptance criteria that defines what can be accepted for**: a)** use **or b)**, in the "product" case, for introduction into commerce. For the pharmaceutical industry, such specifications must be designed to ensure that the each *batch* (or *lot*) of drug product manufactured by a given firm meets *scientifically sound* and *appropriate* **specifications** that define the identity, strength, quality and purity of each dose such that, *after the batch (or lot) is released into commerce*, **a)** each dose can validly be represented to be safe and efficacious **and b)** any **USP** (or **NF)** *article* in said *batch* (or *lot*) will, if tested, meet the explicit and implicit commercial requirements set forth in the **USP** (or the **NF**) for that product. [**Note:** The term controls includes both the equipment used to effect the control required and the permissible limits, ranges, and/or acceptance and other criteria used to establish that a given control is functioning or has functioned as it was designed to function.] A **specification** *is* a predefined characteristic, or limit, or range of an attribute or variable that defines what is an acceptable product outcome for a given process step. Examples of attributes are:

- Comparative degree of whiteness against some set of "white" standards, and
- Degree of perfection (for tablets, un-chipped, chipped, scratched, marked, spotted, specked, miss-punched, cracked, de-laminating, and broken).

Examples of attribute characteristics are:

- Color and
- Shape.

Examples of limits and ranges for tablet attributes include:

- No blue or broken tablets in any *representative* 1250 examined, and
- NMT 3 chipped or cracked tablets in any *representative* 800 examined.

Examples of variables are: content, active release rate, and weight. Examples of limits and ranges for variable factors include:

- Active level is 100 % to 102 % of the label claim (*LC*),
- After 1 hour, *not less than* 10 % *LC* nor *more than* 30 % *LC* is released and, after 4 hours, *not less than* 70 % *LC* nor *more than* 80 % *LC* is released
- Tablet weights must be between 190 and 210 mg.

Specification Limit *is* a predefined upper limit, lower limit, or range that, *for a given characteristic (attribute or variable) factor*, defines what is an acceptable product outcome for a given process step. Examples of limits and ranges for acceptable product outcomes include:

- Acceptable *batches* contain ***NMT*** 3 chipped tablets in any 2500-unit *sample*,
- The acceptable *purity* for a *batch* of Primidone is 99 % to 100 % by weight.

Static sampling *means* the controlled removal of any portion of a **population** for retention and/or testing purposes from the entire **population** after a given production step has been completed.

Statistical inference *means* making generalizations about the characteristics of a **population** derived from the study of one or more **representative samples** from the **population**. **Statistical inference** takes two forms:

- *Estimates* of the magnitudes of **population** characteristics and
- *Tests of hypotheses* regarding **population** characteristics.

Thus, **statistical inferences** are predictions of what would be the case if the parent **population** were fully analyzed with respect to the **characteristic** or **characteristics** evaluated. In the world of drug products, the most common distributions found are the *normal* or *Gaussian*, the *skewed Gaussian*, the *Poisson* and, in multi-station production equipment, *multi-modal* (usually *bimodal*). **[Note:** The bimodal distribution is typically caused by tooling and setup differences or operational problems during the production of a given *batch*.] To simplify discussion, this discussion will presume that the distribution of an in-control pharmaceutical component, material or process product can validly be approximated as a *normal* or pseudo-*normal distribution*.

Target assay, target content or target *refers to* the intended strength or intended amount of active ingredient in the dosage unit that meets the requirements set forth in 21 CFR 211.101(a).

Test, as a verb, *means* to examine something in order to ascertain the presence of or the properties of a particular substance – ***test*** *for bacteria on a surface or* ***test*** *for the level of water in a drug substance.* Test, as a noun, *means* a procedure or method used to **evaluate** a **sample** or **sample** aliquot for some **characteristic** or **characteristic** level – *the test for Chloride was negative*.

Variable *means* something that is capable of changing or varying and, in the pharmaceutical industry, the **variables** are those control and material **factors** that are known to control or contribute to the *variability* in the product produced by a given process.

Weight correction *is* a mathematical correction to validly normalize the content result obtained for the level of active in a "freshly formed" dosage unit to what that active content result would probably have been had that dosage unit been formed at the manufacturer's established target weight. [For example, a tablet with a measured strength of 19.4 mg and weight of 98 mg has a weight fraction active content of 0.197_{959184} mg_{Active}/mg_{Tablet} (mg_{Active} /mg_{Tablet} = 19.4 ÷ 98 = 0.197959184 ~~mg/mg~~). If the drug-product's label claim is 20 mg per each 100 mg tablet, the weight-corrected result percent of active in the dosage unit tested is 0.197_{959184} $~~mg_{Active}~~/~~mg_{Tablet}~~$ ÷ 0.20 $~~mg_{Active}~~/~~mg_{Tablet}~~$ * 100 ~~%~~ = 98.9_{795918} % of the label claim. Rounding that result to two decimal places and using the result to estimate the content of active in the blend that went into that tablet, you find that the blend content was probably 99% of the blend's target content level for the active.]

"**ATTACHMENT 1**" and "**ATTACHMENT 2**"

> For the Attachments, **Lines 609-665**, this reviewer again suggests that the Agency delete these from the draft because its stated scope is to provide guidance for all of the "requirements of 21 CFR 211.110" and not, *as the published draft does*, to simply determining the uniformity of the active content in the samples tested which, as any competent scientist knows, is a necessary, but not sufficient requirement, for compliance with **21 CFR 211.110(a)**, "to assure uniformity and integrity of drug products … of each batch."

IF: a) the Agency's intention is to only provide guidance for the *batch uniformity* of the active or actives in a given material or given units of materials, and
b) not of the overall batch uniformity for all critical variable factors as **21 CFR 211.110 clearly** requires,

THEN: This reviewer again suggests that the Agency published (in Public Docket 2003D-0493 on 30 January 2004) draft guidance title:

"**Guidance for Industry**

Powder Blends And Dosage Units — In-Process Blend And Dosage Unit Inspection (Sampling And Evaluation) For Active Uniformity"

should be used as the *basis* for that guidance.

This suggestion is made because the existing draft is neither *scientifically sound* nor does it meet the in-process CGMP ***minimums*** set forth in **21 CFR 211**.

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

C-04 Comments By PQRI, Dated March 5, 2004

The reviewed PQRI comments begins by stating:

"On behalf of the Steering Committee and the Board of Directors of the Product Quality Research Institute (PQRI), I am pleased to forward comments on the FDA Draft Guidance referenced above.

The attached comments are the result of a review of the FDA Draft Guidance on Blend Uniformity Analysis made by the PQRI Blend Uniformity Working Group, the authors of the original recommendation submitted to FDA in March 2002 and subsequently revised and resubmitted in March 2002 addressing the FDA's questions and concerns."

> Based on the comments here, the PQRI clearly understands that the guidance needed is guidance on uniformity (as the PQRI characterize the published draft guidance as "FDA Draft Guidance on Blend Uniformity Analysis").
>
> [**Note:** However, contrary to the PQRI's statement, the revised draft was not submitted to the FDA in 2002 but rather late in 2003 and it does not address overall uniformity as required by the applicable CGMP regulations – choosing instead to address only the assessment of active uniformity instead of overall uniformity in a manner that is not even CGMP compliant for the assessment of active uniformity.]

The PQRI letter continues by stating:

"The attached document reflects the views of the Working Group and PQRI. We, therefore, request that the comments be included with the other public comments now posted on FDA docket # 03D-0493, noted above,"

> This reviewer simply notes that, *at the time this letter was written*, the only comments posted to the Agency's Public Docket 2003D-0493 were those posted by: a) Hikma Pharmaceuticals ("C-01") and b) FAME Systems ("EMC-01," "EMC-02," and "EMC-03").

Since the PQRI then provides its comments in tabular form, this reviewer has inserted his review remarks after each entry in the tables they provided.

Page #	Line #	Comment
2-4	58-105 Section III/ Scope	The following lines are suggested for suggestion in the Scope: After Readily Passing all validation batches (see Attachment 1), products that are allowed to meet USP requirements using content uniformity by weight variation are exempted from future routine blend testing requirements. Comment: The PQRI report to the FDA recommended the exclusion from the requirements of the guideline those products where the determination of the dosage-unit uniformity by weight variation is allowed. The former BU draft guidance for ANDA products also excluded these products. Not to exempt these products once they meet Readily Pass requirements will place an unnecessary burden on industry that is not required under current regulations. Reviewer's remarks: 1. The commenter seems to knowingly mischaracterize this draft guidance as a "guideline" which it clearly is not. 2. As far as this reviewer can ascertain, there is no part of the CGMP regulations that excludes any drug product from any of the applicable in-process requirements set forth in **21 CFR 211**. 3. Properly, the commenter's "validation batches" should be "initial **process conformance batches**" to conform to the recent change to the FDA's CPG 7132c. (CPG 7132c.08).

Page #	Line #	Comment
2-4 (Cont.)	58-105 Section III/ Scope (Continued)	(Continued) 4. Moreover, *from a scientific point of view*, it is, *if anything*, more important to establish the overall uniformity of the blends, formed dosage units and the finished drug product for those drug products that, ***only* post-release**, the **USP** exempts from having their content uniformity directly evaluated than for those drug products that the **USP** does require to be evaluated for content uniformity. 5. The PQRI's focus on *content uniformity* as if it were sufficient to establish overall uniformity is, at best, misplaced, and factually incorrect. 6. *To properly assess uniformity*, the uniformity of such variable factors as active availability, lubricant level, and, in some cases, stabilizer level, preservative level, level of one or more impurities, residual solvent, water, and other such variable factors must be established. 7. *Unless this commenter believes that recent hundreds of millions of dollars in direct costs and consent decrees borne by some in industry firms for their failures to maintain the uniformity of their batches of products are of no consequence*, recent history would seem to indicate that "assuring the uniformity and integrity" of **all** drug products as **21 CFR 211.110** requires is what is needed. Based on all of the preceding, this reviewer finds that the commenter's suggestions here should be rejected.
3	Footnote 6	Pat guidance published in September 2003, not August 2003 This reviewer agrees with the commenter here.
4	133	… designs of powder sampling *devices* and the--- This reviewer has no problem with the insertion of the word "devices" between "sampling" and "and" here.
5	153-157	Text sounds like additional sample locations should be taken in addition to the 20 stated in the bullet above the text (line 150). This is not the PQRI recommendation. This may also be construed to conflict with the text in lines 254-256 ("There should be at least 20 locations with 7 samples at each for a minimum total of 140 samples." *As written*, there is no conflict between the text in lines 153-157 and the text in line 150 <u>because</u> the text in line 150 sets a "minimum of 20 …"
6	194-196	Text recommends assessing the uniformity of the blends, in-process dosage units and finished product independently. The philosophy of the PQRI recommendation was to assess blend and in-process dosage units jointly, as evidenced by them being contained on the same flow diagram for the validation approach. It is unclear to this reviewer what course of action, if any, the PQRI is suggesting with respect to the draft published by the Agency. However, this reviewer supports the Agency's position that the **uniformity** of the ***blend* from *each phase* of manufacturing**, and <u>not</u> (as this guidance suggests) <u>only</u> the ***final blend***, is required to be appropriately assessed (**21 CFR 211.110**). As a recent Pfizer-released article in the March 2004 issue of **Pharmaceutical Technology** (**24**. **No. 2**, pages 110, 112, 1114, 116, 118, 120-122) by T. P. Garcia, A Carella, and V. Panza, "Identification Of Factors Decreasing the Homogeneity of Blend and Tablet Uniformity," clearly found, the uniformity of a "preblend" was key to establishing apparently appropriate uniformity for the active in the final tablets.

<table>
<tr><th>Page #</th><th>Line #</th><th>Comment</th></tr>
<tr><td>6
(Cont.)</td><td>194-196
(Continued)</td><td>(Continued)
Initially, the uniformity of this “preblend’ under the original preparation conditions was found to be inadequate (with units having active results from 62.9 % to 116.1 % with an average $RSD_{Sample\ [10,2]}$ of “11.4 %”; after improving the preparation of this preblend, the preblends’ active results ranged from 95.7 % to 99.7 % with an average $RSD_{Sample\ [10,2]}$ of “0.61 %”!
After the preblends’ uniformity was improved, among other improvements (in tablet strength and weight, the uniformity of the tablets), the uniformity of the tablets tested was significantly improved and the tablet means, as they should were “100 %” of the target even though the sampling uncertainty for the blend samplings failed to detect any significant blend uniformity improvement.
<table>
<tr><th></th><th></th><th></th><th>Sample</th><th>Est. Batch</th></tr>
<tr><th>Sample ID:</th><th>Mean</th><th>Range</th><th>RSD [n,m]</th><th>RSD Range</th></tr>
<tr><td>Blend before</td><td>98.4</td><td>95.7 — 102.4</td><td>1.9 [30,1]</td><td>1.4 - 2.4</td></tr>
<tr><td>Blend after</td><td>96.15</td><td>92.6 — 100.2</td><td>2.2 [30,2]</td><td>1.8 - 2.6</td></tr>
<tr><td>IBC before</td><td>96.5</td><td>89.8 — 110.9</td><td>2.3 [30,1]</td><td>1.7 - 2.9</td></tr>
<tr><td>IBCs after</td><td>95.9</td><td>91.1 — 105.2</td><td>2.6 [36,2]</td><td>2.2 - 3.0</td></tr>
<tr><td>Tablets before</td><td>97.8</td><td>83.1 — 109.6</td><td>5.0 [81,1]</td><td>4.2 - 5.8</td></tr>
<tr><td>Tablets after</td><td>100.0</td><td>92.4 — 109.7</td><td>3.2 [60,2]</td><td>2.8 - 3.6</td></tr>
</table>
Unfortunately, <u>neither</u> the PQRI’s recommendation <u>nor</u> the Agency published draft guidance forthrightly addresses the issues of uniformity for those ingredients that affect the active availability in the dosage units and the drug product as well as that of other variable factors known to adversely affect drug product quality.
Ignoring the uniformity of those variable factors (or their surrogates) in the blends that control active availability and the uniformity of the active availability (Dissolution and Drug Release) is odd because many drug product recalls are attributable to “dissolution failure” than to “content non-uniformity” per se.
Based on all of the preceding factual realities, this reviewer not only agrees with the Agency’s separation of the uniformity of the blends and that of the dosage units but also urges the Agency to either address active availability and other critical variable in this guidance or recast this guidance as a guidance strictly limited to “Actives Uniformity” with the understanding that the industry must develop their own scientifically sound and appropriate representative-sample approaches to address the other key variable factors that 21 CFR 211.110 clearly requires the firms to assess for uniformity in each and every batch.</td></tr>
<tr><td>6</td><td>199</td><td>Line 199 should be rewritten as follows:
“…10 sampling locations in the blender or discharged bin which include areas of potential poor blending…”
While this reviewer agrees that the commenter’s revision is an improvement, it is still at odds with sound inspection science <u>nor</u> does it address sampling from IBCs.
Based on this reviewer’s understanding of CGMP and “good” practice in blenders and IBCs, a minimum of 20 locations is generally required to fully characterize a bulk mix and top/middle/bottom samples should be sampled when the blend is stored in “drums.”</td></tr>
</table>

Page #	Line #	Comment
6 (Cont.)	199 (Continued)	(Continued) Moreover, the entire sampling approach needs to be revised to take unbiased *batch-representative* blend samples large enough for: **a)** an adequate reserve and **b)** *all* required evaluations for *all* critical variable factors and a *batch-representative number of unbiased unit-dose* (or smaller) *aliquots* (*minimally*, two from each sampled sample) from each sample evaluated for each variable factor for which **21 CFR 211.110** requires the manufacturer to assess its uniformity as well as *truly batch-representative dosage-unit samples* of sufficient number for: **c)** an adequate reserve and **d)** all required evaluations for all critical variable factors (typically, a minimum of 1800 to 2500 or more dosage-unit samples should be taken from each sampled dosage stage where quantitative evaluation of multiple factors should be conducted unless the theoretical batch size is less than 150,000 dosage-units) and the appropriate number of *batch-representative* units evaluated for each critical variable factor by choosing, *at random*, an appropriate fraction of the total number of the units to be evaluated for each test from each sample sampled. Hopefully, the commenter and the Agency will carefully read this reviewer's remarks and revise their understanding of what is required and this draft to meet the strictures of the clear in-process CGMP regulations starting at **21 CFR 211.110(a)**, "To assess uniformity and integrity of drug products, …" and including the in-process requirements set forth in the highlighted portion of **21 CFR 211.160(b)(2)**, "Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. **Such samples shall be representative** and properly identified."
7	210	The BUWG recommendation states at least 10 locations for tumble blenders and at least 20 locations for convective mixers. In the previous line (209), we use (n) ≥10; to be consistent for convective mixers, the text in line 210 should read n ≥ 20. Other than to recommend that the Agency's reviewers improve the grammatical consistency of the preceding statement, adjust the minimum number appropriately upward for tumble blenders (to ≥ 15) and strongly discourage the use of static fixed-shell convective blenders, this reviewer agrees with the commenter that the "=" in line 210 should be changed to "≥" and the minimum number increased from 20 to 30 or more.
Revised Text	216	The following revision of the revision is suggested: If samples do not meet these criteria, we recommend that you investigate the failure according to the flow chart in Attachment 1. Assay the remaining replicate blend samples. To aid in investigating the cause of the failure, dosage form samples (seven form at least 20 locations) may be analyzed. These samples should have been obtained following the procedures described in Section VI, Verification of Manufacturing Criteria. If the cause of failure is not because of mixing, but is attributed to sampling error or other problem(s) unrelated to the homogeneity of the blend, we recommend that you proceed with the evaluation of the dosage form data as described in Section VI. (Continued on next page)

Page #	Line #	Comment
Revised Text (Cont.)	216 (Continued)	(Continued) Though it is not clear to this reviewer as to exactly what the commenter's suggestions are and whether or not the following statement in Lines 217-218, "We also recommend that you not proceed any further with implementation of the methods described in this guidance until the criteria are met" is appropriate, this reviewer cannot support the commenter's suggestions for the same reasons as those presented in the reviewer's responses to similar Lilly comments. In addition, *as written*, the guidance permits the use of failing materials in a subsequent manufacturing phase (dosage-unit-forming), a move that violates one of the basic precepts of CGMP – that failing materials shall not be used in a subsequent step until the cause of the failure is identified and removed, and the "corrected" (reprocessed or reworked) material evaluated and found to meet all of its pre-established acceptance criteria. --- Comment: Attachment 1 needs to be slightly revised to conform to this change in wording. The box containing the text, "Assay at least seven dosage units per each location, weight correct each result" should be moved to be just under the box containing the text, "Assay 2nd and 3rd blend samples from each location" Though the changes proposed do align the text and the attachment, this reviewer does not support the published draft's or the commenter's revised draft's language because it is at odds with: **a)** the requirement ***minimums*** of the in-process CGMP regulations for drug products that the overall uniformity be assessed not just the content uniformity of the active or actives, **and**, in general, **b)** the basic precepts of inspection science that requires the evaluation of a sufficient set of unbiased *batch-representative samples* for each critical variable factor in a material – not just for one such factor, content uniformity, when there are clearly other critical variable factors that should be evaluated.
7	220-234	Should be moved to introduction , immediately after line 197 … "exhibit and/or validation batches". This will allow for alternatives to blend sampling when it is demonstrated during development that blend sampling analysis does not provide useful information. This reviewer cannot agree with what the commenter suggests because it flies in the face of the fundamental precepts of inspection science that require you to correct your flawed sampling and evaluation plans whenever the sampling and evaluating variability is so high that it obscures the underlying level of the uniformity of the material. Given the availability of robotic sampling devices and Class IV isolator technologies when the blend is so toxic that there is no safe way for humans to sample it, this reviewer knows of no sound justification for the failure of a manufacturer to develop a formulation, blending process, and sampling and evaluation procedures for the control thereof that permit valid blend uniformity assessment.

Page #	Line #	Comment
7 (Cont.)	220-234 (Continued)	(Continued) Moreover, in this reviewer's experience dealing with pharmaceuticals as simple as a single active to 30 plus actives (at levels from ppms to 20 %) at scales up to 1 metric ton, this reviewer knows that valid blend sampling (from containers when the scale is large) of multiple-component mixtures can and does provide useful information – including, in some cases, that the blend is not nearly uniform enough for one or more critical variable factors. Based on the preceding, this reviewer urges the Agency to summarily reject: a) such wrong-headed suggestions as those the commenter has suggested in this case just as, b) *except for small-scale (about 5 kg or less) mixing*, the continued advocacy of direct *unit-dose sampling* (*with all of its* known biases) from the blender or the IBCs. [**Note:** *Scientifically sound inspection science* **clearly** supports the sampling of larger unbiased samples in a manner that the subsequent transfer and handling steps do not bias the blend sample's uniformity and from which properly trained analysts can *easily* be trained to take multiple unbiased unit-dose aliquots from each of such multiple-dose sample]
7	241	Guidance recommends that you assess the normality of the data. At our March 2002 meeting with the Steering Committee, Jerry Planchard presented slides stating that if the data is not normal, it becomes harder to comply with the PQRI acceptance criteria. This reviewer agrees with the commenter's statement here but also notes that evaluating non-population-representative samples, or an insufficient number of *batch-representative* samples, or failing to have some measure of the variability contribution of the evaluation method used and/or that of the evaluation process itself, all make it harder to set *scientifically sound* and *appropriate* specifications much less comply with even the PQRI's less than CGMP-appropriate "PQRI acceptance criteria" for active CU – which is clearly not the same as the CGMP-requisite *batch uniformity*. IF the PQRI truly wishes to evaluate the distribution of the CU values, THEN, *based on the sample requirements for distribution-free evaluation, not less than* 300 dosage units should be evaluated for CU.
7	244	RSD for marginally pass should be expressed as $4.0<RSD\leq 6.0\%$ This reviewer cannot support the proposed values or, for that matter, the schema proposed because, in general, a) an insufficient number and/or non-representative samples are evaluated and b) the limits proposed are not appropriate for today's CGMP where all materials are, or should be, expected to produce dosage units whose factor levels are ***expected*** to fall within "± 6 sigma" of their targets. [**Note:** In this reviewer's experience, the limiting active RSD_{Batch} for blends is on the order of 1.0 % with limiting RSDs for the ***samples*** tested on the order of 1.2 % when 30 or more *batch-representative* units are tested. Similarly, for active CU, presuming the limiting weight uniformities for tablets weighing 100 mg, or more, is on the order of 1 % and the limiting transfer RSDs are on the order of 1 %, the limiting $RSD_{CU\ Batch}$ for tablet products is on the order of 1.5 %. Similarly, based on this reviewer's experience, the limiting batch uniformities are on the order of 2 % for capsule CU. The limiting batch RSDs for active availability (dissolution and drug release) are on the order of 0.3 % to 1.2 % higher than those for CU. This reviewer lacks sufficient experience with other critical variable factors to postulate general "rules of thumb" for the limiting RSD values for such factors.]

Page #	Line #	Comment
Revised Text	260	Analyzing a dataset for normality without regard to location may not provide insight into the underlying root causes of the non-normality. Non-normality can be exhibited in both within-location residues, and in location means. The type and extent of non-normality seen in these components, when used in conjunction with a root cause tool such as Ref. 13 in this guidance, will be helpful in not only determining the possible causes of the non-normality, but also establishing if the process is under appropriate blend control. The commenter's unfocused and non-parallel ruminations do change what they recommend be said. However, in general, *since their sampling plan fails to ensure that the samples sampled and evaluated are either point-or batch-* ***representative***, the commenter's remarks here should be discounted, or the entire text revised to be a CU ONLY guidance that is based on full science-based CGMP compliance – NOT the incomplete or non science presented in this part of the Draft.
8	260-261	Same comment as above (for line 241) regarding normality. This reviewer has the same concerns as those he expressed in his review of the commenter's remarks "for line 241."
9	294	…(for one batch n ≥140) the RSD is >4.0 % but ≤ 6.0 percent. Also, this statement implies that if the RSD is > 4.0%, you must test the remaining 80 dosage units dosage units. This inconsistent with the PQRI recommendation that stated an acceptance criteria of ≤6.0%. The product would be classified as being marginally passes because RSD is > 4%. It is unclear what would happen if analysis of the additional 80 samples (should someone elect to do so) results in an RSD ≤ 4.0%. Is the batch classified as readily passes, or still marginally passes? This reviewer is at a loss to see where the "remaining 80 dosage units" come from when the stated sampling plan speaks of 20 sampling points and 7 samples per sampling point. If 20 points are used then 11 units would need to be sampled from each point (20 points x 11 units/point = 220 units) with an initial evaluation of 7 units of the 11 units sampled for each sampling point followed by a second stage in which the remaining 4 units/point would be tested. However, the draft text does not speak of sampling more than 7 per point. Thus, this reviewer is at a loss to make any cogent suggestion since the commenter's suggestions are obviously less than clear. Moreover, until: **a)** the guidance's scope is narrowed to ONLY address CU, **b)** the sampling and testing plans offered are improved in a manner that ensures that more than an adequate number of truly *batch-representative samples* are sampled and tested, **c)** *scientifically sound* and *appropriate* specifications for the sample mean (*not less than* "100 %" of the final target level), range (appropriately inside of the **USP**'s *post-release* expectation of "85 % to 115 %" of the target) and $RSD_{Sample\ (n > 41)}$ is *not more than* (NMT) 3.0 % (for n = 200; RSD NMT 3.2 [for "6-sigma" firms, for n = 60, RSD_{Sample} is NMT 2.25 %; for n = 200, RSD_{Sample} is NMT 2.4 %]), **and d)** appropriate *statistics-based batch acceptance criteria* are established and used, the draft's guidance text cannot be CGMP compliant.

Page #	Line #	Comment
10	365	PQRI recommendation had criteria for the RSD of ≤6.0% for stage 2 testing during routine production (n ≥ 30). Should clarify that the batch would still meet acceptance criteria if 5.0<RSD≤6.0%, but MCM testing would need to be performed. As the preceding review remarks point out, the criteria established by the draft guidance and the commenter's remarks are not valid on the face for the reasons stated in the reviewer's remarks to the Line 294 comments as well as the blatantly specious claim that sample RSD is, in and of itself, a valid batch acceptance criteria when, in point of fact, it is not valid to directly use a sample statistic as a batch acceptance criteria as the language in **21 CFR 211.165(d)** clearly illustrates because that regulation states (**bolding** added for emphasis), "**Acceptance criteria** for the sampling and testing conducted by the quality control unit **shall be adequate to assure that batches** of drug products **meet each appropriate specification** and **appropriate statistical quality control criteria as a condition for their approval** and release. The **statistical quality control criteria shall include appropriate acceptance levels** and/or appropriate **rejection levels**." Even allowing that the sample criteria meet the "appropriate specification" for the uniformity of the active or actives (one specification set), where are the "appropriate statistical quality control criteria" for the batch? Where is the appropriate acceptance level established (0.1 %, 0.5 %, 1 %, 2.5 %, or what percent nonconforming)? Where are the *scientifically sound* and *appropriate* justifications for the inspection plans proposed? How can this guidance ignore the recognized consensus standards (ANSI and ISO) that are clearly applicable to assessment of the quality level of batches of freshly formed dosage units and batches of the finished dosage units? Where are the scientifically sound and appropriate justifications for the specifications proposed? Until this guidance appropriately answers the preceding questions and is clearly restricted to "uniformity of the active or actives" and not batch uniformity for each stage in the process addressed therein, this reviewer is forced to reject this portion and most of the draft as proposed.
11	385	… compare this with the MCM criteria: This reviewer agrees with the commenter's suggested change from the point of view of self-consistency and text accuracy. However, this reviewer continues to oppose the continual mischaracterization of active CU sample criteria as being appropriate to determine the overall uniformity of a *batch* – clearly active uniformity for a small set of samples *is* not, *as the draft guidance asserts and/or implies,* the same as *batch uniformity* or, for that matter, the probable *uniformity of the batch* with respective to the active or actives assessed.

Page #	Line #	Comment
11	405	…and each batch has an RSD of ≤ 5.0%. From only the point of view of text accuracy, this reviewer agrees with the commenter's suggested change. However, this reviewer continues to oppose the continual mischaracterization of active CU sample criteria as being appropriate to determine the overall uniformity of a batch – clearly active uniformity for a small set of samples is not, *as the draft guidance asserts and implies*, the same as batch uniformity. Moreover, *in this instance*, it is clear that the *samples*' "content uniformity" RSD (obtained from the assessment of the active uniformity for some small sample set [< 0.1 % of the batch]), *as is the case here*, is not, and cannot validly be represented to be, the *batch*'s "content uniformity" RSD ("each batch has an RSD of …" much less as the overall uniformity of the *batch* as the language here clearly asserts.
11 -12	423 – 424	These lines seem to require that the data in a submission be normally distributed. This is inconsistent with the revised line 260 that only requires the normality of the data be evaluated. Non-normal data does not necessarily imply inadequate blend uniformity. The type, source, extent and possible consequences of the non-normality must be evaluated on a case-by-case basis. While this reviewer cannot disagree with the commenter's obtuse statement, IF the distribution is not uniform and near normal, THEN, at a minimum, a firm should test *not less than* (NLT) 300 *batch-representative* dosage units and not the **USP**'s 30 dosage units or, for that matter, the consensus standards' normal inspection plans (where 42 to 200 dosage units need to be tested from each batch for the assessment of the active's uniformity). Factually, the concept of uniformity *presupposes*, *for processes of the type covered by the drug-product CGMP*, the output of any acceptable processing step should be uniform. Thus, *when the distribution is not uniform*, it should be obvious that the finding of a non-uniform distribution should cause the step that produced it to be thoroughly investigated and not allowed to proceed until root-cause corrective steps have been taken and the non-uniformity found eliminated by additional processing or alternate processing. Moreover, to define the true distribution of a material, hundreds of samples need to be tested – many more than the "30" that this commenter supports as the "upper limit" for "routine" batches. The recognized applicable consensus standards of ISO or ANSI require numbers larger than this for batches of dosage units larger than 150,000. Based on all of the preceding, this reviewer finds that, in general, since the testing of 200, or more, is the 'NORMAL" sampling level for the "process variability unknown—SD" case in said consensus standards, the guidance proposed should have required that at least that number of dosage units must be tested before a decision can initially be made as to the disposition of a process stage output of dosage units for "routine" batches of dosage units larger than 150,000 for active uniformity and not the 30 units that the draft suggests.

Page #	Line #	Comment
13	478	Add target strength to definition as target assay and target strength are both interchangeably This reviewer does not disagree with the commenter's suggestion here. Factually, the terms "target assay" and "target strength" can both be defined as the draft guidance has defined the term "target assay." However, "target strength" is the more appropriate term and it, not "target assay," should be used throughout this guidance
15	No Line	Note: This comment applies to revised flow-chart. In both the Continuous Routine Testing Using Standard Criteria Method (SCM) and Marginal Criteria Method (MCM) boxes at the top of the flow charts, STM and MTM acceptance criteria should be changed to SCM and MCM. This reviewer supports the need to correct the acronyms in the flow diagrams provided to be consistent with the text though this reviewer continues to note that: a) the flow diagram in question is, at best, ONLY appropriate for the determination of the one aspect of the uniformity of the batch – content uniformity of the active or actives and not, as stated, batch uniformity and b) the decision criteria proposed are neither *scientifically sound* nor *appropriate* – even when limited to the content uniformity of the active or actives in each batch.

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

C-05 Comments By Schering Plough, Posted 9 March 2004

The Schering-Plough comments begins by stating:

"Schering-Plough has reviewed the above referenced Draft Guidance, and we offer the following comments for your consideration."

The Schering-Plough's reviewed comments are as follows:

"We have two general comments applicable to the entire document. The terms have specific statistical meanings, therefore we recommend the more general terminology with a flexible method of evaluation be used; e.g., 'relating,' 'compare,' or 'associate.'"

> This reviewer agrees with the commenter that the terms "correlate," correlation," and "correlating" have specific statistical meanings and supports the appropriate substitution with more general terms, derived from the root words, "relate, " "compare," or "associate," where such substitutions are appropriate in this guidance.
>
> However, this reviewer is unable to ascertain from what the commenter stated what the commenter means when the commenter states, "with a flexible method of evaluation."

"The terms 'locations' and 'intervals' are used interchangeably throughout this guidance, we suggest that one term be used for consistency."

> This reviewer does not disagree with the commenter's suggestion here and would suggest that the appropriate general terminology should be "sampling points" or "points" for time-based sampling (for the dosage units) and "locations" for position-based sampling (for the blends and dosage units sampled after the forming step is completed) be used if the Agency chooses to adopt the commenter's suggestion.

"The remaining comments reference specific sections of the Draft Guidance.

Section III. SCOPE

This guidance will be difficult to apply to bi-layer, tri-layer, and compression coated tablets because an accurate measurement if each layer's weight cannot be determined with the weight correction requirement. We believe the scope of this guidance should be limited to single-layer tablets."

> This reviewer supports the commenter's suggestion here and again notes that, for the drug product portions, the guidance should also be restricted to:
> a) Those drug products that are not "coated" with an active ingredient and
> b) Active uniformity and not overall uniformity (of blends, formed dosage units, or finished dosage units) as the guidance currently claims.

"Section IV. CORRELATION OF IN-PROCESS STRATIFIED SAMPLING WITH POWDER MIX AND FINISHED PRODUCT

A. Assessment of Powder Mix Uniformity.

To promote efficiency and consistency in the development process, selection of the sample size should only require analysis and explanation if quantities larger than the historical 1-3X are used."

Provided:

a) the preceding "sample size" is limited to the ***samples sampled***,

b) the "sample size" for the evaluation (testing) of the samples sampled remains "unit dose or smaller,"

c) the ***samples sampled*** are from *unbiased* samplings and

d) the ***samples sampled*** are sufficient in size to allow for a "reserve," where such is required, and the withdrawal and evaluation of three times the number of singlicate, duplicate or higher replicate "unit dose" aliquots from each sample that the firm's CGMP-compliant "test procedures" require for determining the uniformity of all in-process materials sampled at the end of any phase of manufacturing with respect to ***all*** of that material's ***critical variable factors*** as required by **21 CFR 211.110** – not just "active content" as the present guidance does,

this reviewer concurs with the commenter's suggestion here.

"In addition, it should be acceptable to follow a standard sampling method and size such that additional development will only be required on an exception basis for new products."

Without being presented with a ***scientifically sound*** *inspection plan (sampling and evaluation) that the commenter has established to be appropriate*, this reviewer cannot support the commenter's broadly worded and inexact statement here.

This reviewer recommends that the Agency requests this commenter to provide a proposed "standard sampling method and size" along with a statistical inspection-based justification that clearly establishes the commenter's proposal is *scientifically sound* and conforms to the CGMP minimums for in-process materials and drug products before the Agency considers this proposal.

"We recommend that line 135 of the guidance be revised to read 'Design blend-sampling plans and evaluate *the results* using appropriate statistical analyses.'"

This reviewer does not agree with the commenter's suggested revision because it *improperly* shifts the focus from evaluating the scientific soundness of the "blend-sampling plans" using statistics to simply evaluating "*the results* using appropriate statistical analyses."

"It is unclear what is the intent of 'Quantitatively measure any variability…' is. Would comparison of RSDs be sufficient?"

Though it is clear to this reviewer what the intent of the statement in Line 136 is (a full variance factor analysis) from the context of the other statements that follow this initial statement in this bullet point, this reviewer leaves it to the Agency to answer the commenter's question here.

"**B Correlation of Powder Mix Uniformity with Stratified In-process Dosage Unit Data**

Line 149 of the guidance requests sampling 'defined intervals and locations.' Please clarify the differences between an interval and a location."

This reviewer offers the following examples in answer to the commenter's request for "the differences between a ~~interval~~ time point and a location" because that is the question that should have been asked:

"**Dynamic**" or "**Time Point**" **Sampling:**

Example:

Beginning when the system meets set-up uniformity, take a "Start" sample, and then, for the requisite "Time Point" samples about every 10 minutes, sample four times the nominal full-cycle output from all of the active dosage forming stations in the dosage forming system until the normal end of production, "End" sample has been collected unless the sampling plan used requires additional or different sampling points, or a processing interruption occurs (this event requires a taking "Restart" sample for each such interruption). In some cases, it may be acceptable to use a "Restart" sample in place of a scheduled "Time Point" sample.

"Static" or "**Location**" **Sampling:**

Examples:

1. Randomly sample not less than 100 dosage units from each drum of in-process tablets from the output of the polishing operation.
2. Sample top, middle and bottom samples from each drum of final blend stored in the IBCs used for holding the batch before it is approved for use in dosage forming.
3. Using Sampling Plan "X," take one 25-g sample from the following locations in the blender at each of there levels (top, middle, and bottom):
   a. Front right,
   b. Center center,
   c. Back left,
   d. Front center,
   e. Center left,
   f. Back center,
   g. Front left,
   h. Center right,
   i. Back right.

   [**Note:** Sample the top, then the middle and finally the bottom level at each location before proceeding to the next location. After blender is emptied, also collect a 25-g sample from the material in the discharge valve as well as a 25-g sample from the material remaining on the inside walls of the blender from each charging port or surface other than the discharge valve.]

"The minimum of 140 samples may be excessive during early stages of development when the batch size is typically small."

This reviewer cannot agree with the commenter's suggestion here for several reasons:

1. Batches smaller than 1 kg are rare, even in development, and even such small batches typically produce in excess of 2000 dosage units.
2. In development, *where the true distribution of the materials is not known*, the number of samples that should be tested should be larger than for routine batches.
3. For the dynamic (time point) sampling specified, the number of samples sampled at each sampling point should be the appropriate integer multiple of the number of dosage forming stations in the dosage-forming equipment used to ensure that the sample sampled is truly *representative* of the batch. [**Note:** In general, this reviewer recommends that the integer multiple should be larger than the number required for a "Reserve" and three times the number required for all evaluations of uniformity for each critical variable factor required to establish the uniformity of the drug product.]
4. The distribution-free minimum number of *batch-representative* units that should be tested is 300.
5. The proposed 140 units sampled is less than that required for *each critical variable factor* for the "process variability unknown, "normal inspection" case in the applicable recognized ISO (ANSI) consensus standards for batches larger than 35,000 dosage units. [**Note:** If, for example, there are four critical variable factors (active content, active availability, lubricant level, and a degradation stabilizer) for the drug product's formulation and a development batch contained only 20,000 dosage units, then, not less than 1500 *batch-representative* dosage units should be sampled (3 times the 100 required for "normal inspection" for each of the four (4) identified critical variable factors that need to be evaluated plus 300 for a reserve. Even in this case, the number of samples is less than 10 % of the batch's total size.]
6. *Except for developmental batches*, this reviewer understands that typically not less than 1800 to 2400, or more, *batch-representative* dosage units should be *sampled* from each stage where dosage-unit sampling is required.

For all of the reasons stated, the commenter's suggestion:

a. Misstates the reality that the published draft's "total minimum of at least 140 samples" grossly understates the minimum number of samples that should be sampled,
b. Fails to address the lack of a *batch-representative* requirement for the samples sampled or, as it should,
c. Does not require that:
   i. an equal number of formed dosage units must be sampled from each dosage forming station at each sampling point and
   ii. said number must ensure that the local variability in the dosage forming process is captured in each sampling point

   so that the sample sampled is assured of being *batch representative* whenever the sampling frequency has been established to be at least frequent enough to capture the variability in the blend used to form the dosage units.

[**Note:** This reviewer notes that many firms routinely take samples of "2500" dosage units and evaluate those samples, against multiple in-house acceptance criteria, for their

critical visual attributes using double the number required by their sampling attribute inspection plans that are based on either the now-superseded MilSpec 105 standard, or the current recognized replacement ANSI Z1.4 (or its ISO equivalent) consensus standard. They do this without any complaint that taking such is excessive. Moreover, after taking such a batch-representative number of dosage units and examining it using non-destructive visual inspection, nothing prevents those samples from also being used as the samples to assess the critical variable properties in the formed dosage units. Thus, it would appear that the commenter's real concern cannot truly be the number sampled. It seems to this reviewer that the minimum number that this Draft suggests should be tested for *each critical variable* is simply more than they want to test. Based on these realities, they obviously are seeking to have the Agency to continue to:

a. Ignore the clear requirements of the drug-product CGMP regulation ***minimums*** for in-process materials with respect to assessing uniformity and

b. "Let" the commenter and the industry test so few samples against non-CGMP compliant *acceptance criteria* to insure that there is no assurance that the *batch* is uniform or meets the other clear requirements established in the drug-product CGMP, and

c. "Let" the commenter and the industry use noncompliant inspection plans designed to ensure that their products' current level of ***batch variability*** remains hidden.]

"Please clarify what is meant by 'significant events in blending process' from line 161. Is this for compressing/filling operation?"

Since, even with duplicate sample blend sampling from as many as five (5) bags of blend in each of 10 or more 50-kg IBCs ("100" sampling locations) where areas of greater (than the targeted level) and lesser uniformities for each critical variable factor may be detected and tracking of the blend used with the formed dosage units produced, the tracking of materials between the blend and the formed dosage units is, at best, inexact, this reviewer would suggest that the text in this bullet be revised to read:

"• Prepare a summary of the data including the specific content values (content values corrected to the target unit or unit-fill weight) for each tablet or capsule tested and the corresponding statistical batch distribution estimates derived therefrom, minimally at the 95-% confidence level, and compare said statistical distribution estimates for the specific content values to the similarly statistical derived batch distribution estimates from the final blend data for the blend used to fabricate the dosage units. ~~and analysis used to correlate the stratified sampling locations with significant events in the blending process.~~ We recommend you submit ~~this~~ a summary of all available data, findings, specifications, acceptance criteria, and investigations for all critical variable factors that bear on the batch uniformity of the in-process blend and formed dosage units with the ~~application~~ submission as described in section VIII of this guidance. In cases where the information from the requisite initial full-scale process conformance batches required is not available, the submission should contain a commitment to submit such when they become available."

" **C. Correlation of Stratified In-process Samples with the Finished Product**

Process validation is not required to be completed prior to submission of the regulatory application, therefore data available for inclusion in the submission should only be pilot scale"

Since the production of initial process conformance batches at full scale can be deferred until after a submission, this reviewer would recommend that this section be rewritten to require the submission of all available data, findings, specifications, acceptance criteria, and investigations for all critical variable factors that bear on the batch uniformity of the formed dosage units and the drug product units. In addition, a commitment should be made to submit all of the similar information from the initial full-scale process conformance batches when such information becomes available.

In light of the preceding, this reviewer recommends that this section be revised to read:

"**C. ~~Correlation~~ Comparison of the Results From ~~Stratified~~ *Dynamically Sampled* In-Process *Dosage-Unit* Samples ~~with~~ To the Results From the Finished Product Samples**

- Conduct testing for uniform content of the finished product using an appropriate CGMP-compliant procedure (**21 CFR 211.160(b)(3)**, **21 CFR 211.165(d)**, and, for controlled-release dosage forms, **21 CFR 211.167(c)**) or**,** when the manufacturer's approved application or license specifies a larger batch-representative number is required to be tested, ~~as~~ the larger number specified in the Abbreviated New Drug Application (ANDA) or the New Drug Application (NDA) for approved products."
- Compare the statistical inferences derived from the results ~~of stratified~~ observed, without weight correction, for the dynamically sampled in-process dosage unit analysis from the previous step with ~~uniform content~~ the corresponding statistical inferences derived from the representative sample results from ~~of~~ the finished dosage units from ~~the previous~~ this step. This analysis ~~should~~ must be done without weight correction.[14]

[14] Weight correction is a mathematical correction to ~~eliminate~~ correct for the effect of ~~potentially variable~~ the tablet weight on ~~measurement of mix adequacy~~ measured tablet content values —see Glossary, Section IX."

- Prepare a summary of the data and analysis used to conclude that the ~~stratified~~ dynamic in-process sampling provides assurance of uniform content of the finished product. We recommend you submit this summary with the application as described in **Section VIII** of this guidance. In cases where the information from the requisite initial full-scale process conformance batches required is not available, the submission should contain a commitment to submit such when they become available."

"**Section V. EXHIBIT/VALIDATION BATCH POWDER MIX HOMOGENEITY**

The recommendation to sample 20 locations to adequately validate convective blenders is excessive. Not less than 10 locations should be adequate to capture worst case locations in convective blenders. Likewise for ribbon blender, not less than 10 should be adequate."

Based on this reviewer's experience with both rotating shell and fixed shell blenders, including ribbon blenders, this reviewer cannot agree with either of the commenter's suggestions.

Moreover, this reviewer cannot recommend the use of most ribbon blenders and would recommend that, because of their design and wear realities, in general, ribbon blenders should not be used for the production of pharmaceutical blends.

Since the CGMP regulations require the sampling of *batch-representative samples* for in-process materials and the drug product (**21 CFR 211.160(b)(2)**), this reviewer cannot support only sampling the putative worst-case locations in a blend.

Similarly, *based on this reviewer's experience*, this reviewer recommends a minimum of 15 batch-representative locations be sampled in most cases but:

1. Does not recommend that the guidance propose a fixed number but, rather, that the guidance should require the submitter to justify the number, location, amount and unbiased nature of the blend samples sampled.
2. For each critical chemical variable factor that is quantitatively evaluated, state that a minimum of two (2) unbiased unit-dose, or smaller, aliquots should be evaluated from each sample sampled, and, for each critical physical property that must be evaluated, state that at least one appropriately sized sample should be evaluated from each sample sampled.

[**Note:** Each sample sampled should be sufficient large in amount to permit the requisite number of unbiased samples to be removed for evaluation for all critical variable factors (chemical and physical) as well as provide a reserve of sufficient size to permit all of the initial chemical evaluations to be repeated up to three (3) times.]

"Please clarify what is meant by 'additional' in lines 225-226."

In the published Draft, the word "additional" does not occur in "lines 225-226" but in Lines 226-227.

If this is the text the commenter refers to, this reviewer suggests that this sentence should be rewritten to clarify what the Agency meant to say here.

This reviewer suggests that the sentence in question should be revised to read:

"In such cases, process knowledge and data from indirect blend uniformity assessment ~~sampling~~ (obtained by *scientifically sound* and *appropriate* inspection [sampling and evaluation or classification] of the blend in the IBCs into which it is transferred) combined with ~~additional in-process dosage unit data~~ the weight-corrected result values and the predicted batch characteristics derived from the testing of *not less than* (NLT) 200 *batch-representative* tablet-core or capsule content samples (the minimum number required for a 95-% confidence-level prediction of the acceptability of the batch) for *each* critical variable factor, including active content, may be adequate to demonstrate the ~~adequacy of the powder mix~~ *the requisite level of blend uniformity*.

"**Section VI. VERIFICATION OF MANUFACTURING CRITERIA**

A. In-Process Dosage Unit Sampling and Analysis

We propose that the wording for lines 262-263 be revised to read '..significantly affect your ability to ensure batch homogeneity, they should be *controlled* (or *accounted for*).'"

In the published (.pdf) file, the lines containing the cited text are Lines 262-264.

This reviewer cannot support the commenter's suggested changes because finding such outcomes (significantly adverse "trends, bimodal distributions, or other

forms of a distribution other than normal") means that one or more steps in the process must be corrected to produce batches that are uniform in distribution.

Instead of the commenter's revision, this reviewer suggests the following:

"If *any of* these ~~occurrences~~ *conditions* significantly affect your ability to ensure batch ~~homogeneity~~ *uniformity*, ~~they should be corrected~~ the root cause or causes for the non-uniformity of the results should be identified, appropriate corrective actions implemented, and the studies repeated until the results indicate that *each batch*, not just the samples tested, is *sufficiently uniform* with respect to the level of *each critical variable factor* in the dosage units."

"**B. Criteria To Meet Readily Pass Classification**

C. Criteria To Meet Readily Pass Classification

Are these to be based on 'weight corrected results' or 'as is'?"

This reviewer knows that, except for estimates of the "weight corrected" level of a variable factor for the purposes of estimating the variability in a material without including the weigh component of that variability, the acceptance criteria for any variable factor, including active content, should be on an "as is" basis.

Further, *unlike the non-CGMP compliant acceptance criteria proposed here*, CGMP-compliant acceptance criteria should be based on the testing of a *batch-representative sample* of sufficient size (amount or number).

In addition, *for in-process materials*, the specifications established should be, as **21 CFR 211.110(b)** states (**bolding** emphasis added), "Valid in-process specifications for such characteristics **shall be consistent with drug product final specifications** and **shall be derived from previous acceptable process average and process variability estimates** where possible and **determined by the application of suitable statistical procedures** where appropriate," but those in this Draft are <u>not</u>.

This reviewer finds that the specifications in the published Draft fail to meet all of the three pre-conditions for CGMP compliance and that the supporting publications also fail to do so.

For the drug product units, this reviewer finds that the Draft's specifications do <u>not</u> meet the CGMP minimums set forth in **21 CFR 211.160**, "General requirements"; **21 CFR 211.165**, "Testing and release for distribution" (including the "statistical quality control criteria" and "acceptance level" requirements of **21 CFR 211.165(d)**, and, where applicable, **21 CFR 211.167**, "Special Testing Requirements", including the "appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient" requirement set forth in **21 CFR211.167(c)**.

For all of the preceding reasons, this reviewer recommends that these sections of the Draft be rewritten to remove the prescriptive limits suggested and, instead, suggest how, in general, a firm should go about developing and justifying the that the "specifications, standards, sampling plans, and test procedures" the firm is proposing are *truly scientifically sound* and *appropriate* for each critical variable factor, including but not limited to, active content, active availability, weight, stabilizer, and other variable factors (e.g., water or residual solvents) that may adversely impact the safety and/or efficacy of the dosage units in each batch.

"**Section VII. ROUTINE MANUFACTURING BATCH TESTING METHODS**

A. Standard Criteria Method (SCM)

For Stage 1 testing, we suggest that at least 7 dosage units should be collected in case the MCM plan required. Otherwise, there may not be sufficient sample collected upfront and it may be difficult to resample the exact same locations."

This reviewer agrees that all samples that should ever be needed should be sampled initially because, as the commenter notes, it is "difficult to resample the exact same locations" should such ever be required.

This is doubly true when the samples are sampled dynamically as the dosage units are being produced.

However, for dynamically sampled samples, that minimum number should be some multiple of the number of dosage-forming stations in the machinery used to form the dosage units – a number that typically is in the multiple tens of dosage units for each sampling point.

"**Section VIII. REPORTING THE USE OF STRATIFIED SAMPLING**

A. Applications Not Yet Approved

We note that this section contains recommendations for submissions, however we remind the Agency that validation studies are not required to be completed prior to application submissions, therefore most of these data would not normally be available."

Except for sterilization process steps where producing and evaluating process conformance batches is required prior to submission, this reviewer agrees with the commenter concerning the current draft and, as previously, proposes that the following should be included with any submission that falls within the scope of this guidance:

1. A certification, by senior management and the head of the firm's quality unit, that:
   a. *Scientifically sound* and *appropriate* data evaluation and statistical procedures were used wherever such are indicated as being usable as well as
   b. The information submitted fully complies with the applicable CGMP *definitions* and *requirement minimums* set forth for drugs in **21 U.S.C. Title 9** and **21 CFR Parts 210** and **211.**
2. All available results data from each processing stage that was sampled for all critical variable factors, arranged by processing stage and critical variable factor as well as the proofs that establish that each set of data for each critical variable factor is *batch representative* and *appropriate* for each variable factor in the set.
3. All "findings," arranged by processing stage and critical variable factor, with respect to the data, including, but not limited to, numbers of samples tested, ranges, means, sample RSDs, medians, modes, variances and variance components (where knowable), projected batch limits, means, and RSDs as well as the acceptability or lack thereof at each processing stage.

4. All *specifications* for each critical variable factor arranged by processing stage and critical variable factor and the scientifically sound justifications that establish the validity of each and every *specification*.
5. All *acceptance criteria*, including, *for the drug product*, statistical quality control criteria that specify the acceptance quality level (AQL) and/or Rejection Quality Level/RQL for each critical variable factor, for each processing stage along with the proofs that establish that the *acceptance criteria* selected by the firm are adequate to predict, at a 95-% confidence level or higher, that the result values for all of the critical variable factors are expected to be within plus/minus "6 sigma" of the target level for each critical variable factor.
6. All investigations that bear on the batch uniformity of each in-process blend, the formed dosage units, and the finished drug product units.
7. A commitment to maintain all of the raw data acquired in any of evaluation of samples and all of the preceding information in a manner that it is readily available for inspection for at least one year beyond the expiration of the last marketed batch of drug product.
8. If not submitted, a commitment to submit all of the preceding for the initial process conformance batches from the initial full-scale "Evaluation (Performance) Qualification [EQ/PQ]" phase of validation.
9. A commitment to maintain all of the supplemented raw data acquired in any supplementary evaluation of samples and all of the preceding supplemented derivative information derived therefrom in a manner that it is readily available for inspection for at least one year beyond the expiration of the last marketed batch of drug product.

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

C-06 Comments By Pfizer Inc, Posted 9 March 2004

The Pfizer comments begins by stating:

"Pfizer would like to acknowledge the effort put forth by the FDA in the publication of the Draft Guidance for Industry on Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment. We would also like to acknowledge the acceptance by the agency of the PQRI recommendations. It is recognized that a great effort has been made to incorporate the draft recommendations of the Blend Uniformity Working Group (BUWG) published in the PDA Journal of Pharmaceutical Science and Technology 57:59-74, 2003.

As a member of PhRMA, Pfizer has contributed to the preparation of the industry comments submitted by PhRMA to the agency. In addition to those comments we would like to submit the following five items listed in the table below."

Pfizer's reviewed comments are as follows:

Section	Guidance Line	Comment	Rationale
IV.B	150-152	Add reference to Attachment 1. There should be at least 7 samples taken from each of these locations for a total minimum of at least 140 samples. (See Attachment 1.) In general, this reviewer cannot agree with the original text much less the addition of a reference to Attachment 1 in an effort, based on the rationale to limit the number of samples to be tested for active content to a number less than the 140 dosage units sampled. This the case because the sampling plans proposed are, in general, not *scientifically sound* and *appropriate* for the evaluation of active content much less for the sampling scenario (dynamic sampling) unless: **a)** the equipment used has either exactly one or seven dosage-forming stations and **b)** there are no other critical variable factors that must be evaluated. [**Note:** In general, other factors (e.g., active availability, weight, water content, residual solvent level, impurities, stabilizers, lubricant level) may be critical factors that should also be assessed.] This reviewer also rejects the premise that determining the uniformity of the active is sufficient to assess the uniformity of each batch when, in fact, all know that it is not – active content uniformity and batch uniformity are NOT synonymous!	Without the attachment, it implies that 140 samples must be tested. Contrary to the Draft's rationale, the valid minimum number of discrete samples to test should be no less than the applicable numbers in the recognized consensus standards that outline minimum, at the 95% confidence level, numbers to test and statistical *batch acceptance criteria* appropriate to the acceptance of various percentages of nonconformance to the *specifications* used. For single-variable-factor, "process variability unknown," "normal" sampling and testing plans, the minimum numbers are 200 *representative* units for batches larger than 150,000 units and 150 units for batches larger than 35,000 units. Thus, the "sampling plans" proposed do not even meet the CGMP minimums for assessing the active's in-process uniformity in the dosage units.

Section	Guidance Line	Comment /Observation	Rationale / Basis
V.		Clarify whether blend uniformity and in-process dosage unit testing is required for all BE/biobatches or only for the full-scale batches or only batches that support implementing the stratified sampling method. Since the CGMP regulations specify assessing the uniformity and integrity of *each batch* of drug product that is administered to humans and animals, and require assessment and release at the completion of each processing phase, the CGMP regulations clearly require *all such batches* to be evaluated *at each phase of manufacture*. This reviewer therefore recommends that the guidance be changed to conform to the *clear* requirement ***minimums*** of the applicable CGMP regulations governing the assessment of a sufficient number of ***representative*** in-process material samples to **ensure the uniformity** and integrity **of each batch** – **NOT**: **a)** Content uniformity of the samples tested for their level of active in each batch or **b)** Batch uniformity of the active or actives in the blend or dosage units in each batch, **BUT:** The overall ***batch uniformity*** for ***all critical variable factors***, including the level of each active, the availability of all actives, content weight, and all other critical variable factors in a given drug product, in ***each batch***.	The commenter provided no rationale. **Reviewer's Basis:** Among other things, **21 CFR 211.110** states: "a) **To assure batch uniformity** and integrity of drug products, **written procedures** shall be established and followed that describe the in-process controls, and tests, or examinations **to be conducted on appropriate samples of in-process materials of each batch**. **Such** control **procedures shall be established to monitor the output and** to **validate the performance of** those manufacturing **processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include**, but are not limited to, the following, where appropriate: (1) **Tablet or capsule weight variation**; (2) Disintegration time; (3) **Adequacy of mixing to assure uniformity and homogeneity**; (4) **Dissolution time and rate**; (5) Clarity, completeness, or pH of solutions. (b) **Valid in-process specifications for such characteristics shall be consistent with drug product final specifications** and **shall be derived from previous acceptable process average and process variability estimates where possible** and **determined by the application of suitable statistical procedures** where appropriate. **Examination and testing of samples shall assure that the drug product and in-process material conform to specifications**. (c) **In-process materials shall be tested for identity**, **strength, quality,** and **purity** as appropriate, and approved or rejected by the quality control unit, **during the production process**, e.g., at commencement or completion of significant phases or after storage for long periods.

Section	Guidance Line	Comment	Rationale
General Comment		Indicate if this guidance is applicable to other unit operations that occur before tabletting or encapsulation, for example fluidized bed bead or granule coating, which is immediately followed by encapsulation. This reviewer understands that, provided the draft is corrected in a manner that renders it CGMP-compliant and either: **a)** focuses it on to be ONLY to assess the uniformity of the active(s) in the batch **or b)** is widened to properly address overall batch uniformity, a CGMP-compliant guidance should include a statement coupled with its factual basis that the guidance furnished for the in-process assessment of the *uniformity* of each batch: A. Is applicable to other unit-operations that meet the CGMP definition of "**significant phases**" B. When Point "A" is met, MAY be used or modified as appropriate provided the output of said "unit operation" or significant phase is intended to produce an adequately uniform material. C. Should be modified, as appropriate, to ensure that the "**specifications, standards, sampling plans, testing procedures**" and other process controls are *scientifically sound* and *appropriate*, supported by a valid body of data buttressed by appropriate non-parametric and normal statistical control evaluations that establish that the output of each "unit operation" or significant phase is uniform. Based on the preceding, this reviewer recommends that the guidance simply state that, provided the justification provided is scientifically sound, the manufacturer **may** be able to apply the guidance furnished to other ***material producing*** "unit operations" that produce *uniform* materials and, in some cases, **may** be able to justify combining them into a single "**significant**" processing phase provided they are not separated by time. However, the firm's QCU must evaluate and release the output of each significant processing phase prior to that output's being used in a subsequent step.	A fluidized bed process can provide mixing such that a subsequent conventional blending step is not required. While this reviewer recognizes, *as evidenced by the "scientific" studies performed to support the noncompliant guidance in this Draft*, that it is easy to misuse statistics, this reviewer also knows that the proper application of first distribution-free statistics and then, *when sufficient data and understanding is acquired and the process reaches the point that the output of each process* ***material-producing*** *"unit operation" is uniform*, the proper application of "normal" statistics can be used to describe the uniformity observed and required and in setting appropriate sample and BATCH *specifications* and/or *acceptance criteria* for the output of each ***such*** "unit operation." When that level of understanding of each ***material-producing*** "unit operation" is reached, the firm may be able to then appropriately combine ***such*** "unit operations" ONLY when they proceed *without interruption* from one such to the next provided the process of going from one ***such*** "unit operation" to the next does NOT risk introducing a significant non-uniformity in the material produced by each prior "unit operation" in ***such*** combined operations. In cases where there is a significant delay between operations and that delay may lead to significant non-uniformity, ***such*** "unit operations" cannot be considered a single significant phase because they are separate (time-separated) phases. It is therefore incumbent on the submitter to justify whatever course of in-process action that it asserts is CGMP compliant. All in-process controls must meet all of the applicable "each batch" component, in-process, and drug-product CGMP ***minimums*** **in 21 CFR Part 211**.

Section	Guidance Line	Comment	Rationale
Glossary	459-460	Provide a better definition of "exhibit batch" In keeping with the 12 March 2004 changes to the Agency's **CPG 7132c** that addresses the Agency's current views in process validation requirements in Sec. 490.100, titled "**Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval** (CPG 7132c.08)," this reviewer proposes replacing all references in this guidance to exhibit batches or validation batches with the policy guide's phraseology, "**process conformance batches**" which *means* any batches that are produced to demonstrate the agreement of the process outputs with their established *specifications* and *acceptance criteria*. In addition, this reviewer suggests that all should carefully consider the statement in that updated policy document that discusses "*process validation*": "Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110), and is considered an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs) under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product. **The proof of validation is obtained through rational experimental design and the evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase**." Thus, as of March 2004, the Agency's position is that validation should begin in the "**process development phase**" (Design Qualification [DQ]) and should continue "**through the commercial production phase**" (Maintenance Qualification [MQ]). Thus, *process validation* does not stop, as many firms currently do, at the "Performance Qualification (PQ)" stage. The Agency's current position seems to be fully aligned with the "to monitor … and to validate …" requirements for each batch as set forth in **21 CFR 211.110**. (Continued in the next page)	Exhibit batches need to be clarified for NDA applicants. This reviewer's bases for the change suggested are contained in the reviewer's remarks.

Section	Guidance Line	Comment	Rationale
Glossary (Cont.)	459-460 (Continued)	(Continued from previous page) Moreover, the amended guide continues with: "Before commercial distribution begins, a manufacturer is expected to have accumulated enough data and knowledge about the commercial production process to support post-approval product distribution. Normally, this is achieved after satisfactory product and process development, scale-up studies, equipment and system qualification, and the successful completion of the initial conformance batches. **Conformance batches** (sometimes referred to as "validation" batches and demonstration batches) **are prepared to demonstrate that, under normal conditions and defined ranges of operating parameters, the commercial scale process appears to make acceptable product. Prior to the manufacture of the conformance batches the manufacturer should have identified and controlled all critical sources of variability.**" Based on the preceding, this reviewer suggest that the definition of "**Exhibit Batches**" be deleted and replaced with: "**Conformance Batches** refers to any batch produced to demonstrate, and that does, in fact, establish the agreement of the process outputs with their expected specifications and established acceptance criteria which is required to be, or should be, submitted to support any DMF, VMF, IND, ANDA, NDA, or, when within the purview of the CDER, BLA. This includes any test, bioequivalence, clinical batch, scale-up batch, technology-transfer batch, change-supporting batch, and commercial production batch that are required to be or should be included with any process-related submission to the Agency."	This reviewer's rationale for the change suggested is contained in the reviewer's remarks that start on the previous page.
General Comment		Indicate that this guidance is not intended for PAT method use. This reviewer agrees with the commenter's suggestion here.	The regimen described in this guidance is not designed for PAT guidance. This reviewer supports the commenter's rationale here.

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

C-07 Comments By PhRMA, Posted 11 March 2004

The PhRMA comments begins by stating:

"The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing more than $30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in search for cures."

PhRMA's reviewed comments are as follows:

"We appreciate the opportunity to comment on the draft guidance on a stratified sampling approach to assess uniformity of powder blends and finished dosage units, which incorporates recommendations from the Blend Uniformity Working Group of the Product Quality Research Institute (PQRI)."

Unfortunately, this reviewer finds that the "stratified sampling approach," defined in this draft guidance by directing the sampling to "locations" where the material is purportedly least uniform, fails to ensure the samples are truly *representative* of the *batch* and therefore fails to comply with **21 CFR 211.160(b)(2)**.

Moreover, the guidance provided is clearly less than *scientifically sound*.

It only provides this less-than-scientifically-sound guidance for assessing the uniformity of the ***active***, or ***actives***, in "powder blends and finished dosage units."

Factually, ***active uniformity*** is only one facet and, for some products (e.g., extended and delayed release drug products), not necessarily the most critical factor in the set of critical variable factors that **21 CFR 211.110** requires a firm to evaluate *each batch* for their uniformity during manufacturing (at each significant phase).

Furthermore, this guidance ignores the CGMP definition of drug product (**21 CFR 210.3(b)(4)**, "Drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo," since the guidance purports to address asserting general uniformity of the final blend and the dosage units for drug products but the guidance provided is limited to assessing active content which cannot be used to assess uniformity in drug products that are placebos.

Factually, the clear requirements of **21 CFR 211.110(a)**, "To assess uniformity and integrity of drug products … of each batch," require a firm to evaluate a *batch representative set of samples* for each and every *variable factor* that "may be responsible for causing variability in the characteristics of in-process material and the drug product"

For tablets and capsules, those variable factors for which uniformity of the in-process materials and drug product obviously include, but are not limited to: "(1) Tablet or capsule weight variation; (2) Disintegration time; (3) Adequacy of mixing to assure uniformity and homogeneity;" and "(4) Dissolution time and rate." (**21 CFR 211.110(a).**)

Moreover, if, *as the Agency appears to state in the Draft*, one restricts the scope of the assessment of uniformity to "(3) Adequacy of mixing to assure uniformity and homogeneity," *one aspect of what the CGMP regulations assert must be monitored and validated*, then to establish "mix uniformity" at the beginning or completion of each significant phase of the manufacturing of each drug product batch, more than active uniformity must be established.

Minimally, a final powder mix for a tablet or capsule drug product typically consists of: **a)** an active, **b)** a release mitigation agent (accelerating or delaying), **c)** a powder lubricant and **d)** a filler.

In this minimal formulation, it is or should be obvious that one must establish the appropriate uniformity of ingredients "**a)**" through "**c),**" or, *where more convenient*, their surrogates, to establish that the mix is adequately uniform – not just the uniformity of ingredient "**a)**" as this draft guidance asserts based on its title and the text in the guidance provided.

Further, for the increasingly common class of extended-release drug products, the uniformity of the active may not be even the most critical variable factor that should be determined to be sufficiently uniform – in many cases, the release-control agent is that factor.

Based on the preceding realities and the clear requirement minimums, as titled, this guidance is fatally flawed and does not provide a CGMP-compliant approach to compliance with **21 CFR 211.110(a)(3)** much less what is truly needed, a CGMP-compliant approach to compliance with the clear in-process requirement ***minimums*** set forth in **21 CFR Part 211** as they apply to simple single-layer tablet drug products and drug products that are capsules filled with blended powders.

To address the draft's obvious shortcomings, this reviewer submitted a proposed revised guidance titled, "**Guidance for Industry Powder Blends And Dosage Units — In-Process Blend And Dosage Unit Inspection (Sampling And Evaluation) For Content Uniformity**," that was published in the FDA's Public Docket 2003D-0493 on 30 January 2004.

"In addition to the attached line-specific comments, we would like to draw your attention to a discrepancy between this guidance and both the PQRI recommendation and the withdrawn draft blend uniformity guidance for ANDA products. The PQRI report to FDA recommended that the guidance requirements exclude those products where determination of the dosage-form uniformity by weight variation is allowed. This recommendation is consistent with the draft ANDA blend uniformity guidance. The scientific rationale for removing this exemption from the current draft guidance is not evident. Furthermore, disallowing this exemption represents a significant increased burden on the industry. We urge you to include this exemption in the final guidance."

Specifically, the exemption being sought, not to assess the uniformity of the in-process blend and formed dosage-unit for the batch variability with respect to any of its critical variable factors is being sought for drug products that the post-release in-commerce requirements set by the **USP** (*which ONLY apply to distributed drug products in commerce*) for uniformity of dosage units permit weight variation to be used in lieu of content uniformity assessment.

The exemption being sought is for the Agency to issue guidance that clearly conflicts with the legally binding, in-process, CGMP requirement ***minimums*** for the assessment of the uniformity of each batch.

To its credit, the Agency has apparently recognized that to do so would be to publish written guidance that plainly conflicts with one or more of the clear binding CGMP regulations for drug products – an activity that the US Supreme Court ruled was an illegal activity in *Berkovitz v. USA* – and declined to follow the PQRI's non-conforming advice.

With respect to the commenter's statement, "The scientific rationale for removing this exemption from the current draft guidance is not evident," this reviewer offers the following observations:

1. When a proposed exemption is illegal, then its supporting scientific rationale, if such were to exist, is of no import.
2. There is no valid sound science that would support not assuring that such drug products are adequately uniform before they are released because there will be no post-release evaluations – don't assure uniformity because the post-release **USP** requirements do not check for active uniformity – an approach that is not only anti-quality and illegal but also ignores the need for the assessment of the uniformity of each "mix" for other critical variable factors.
3. The applicable "**WEIGHT VARIATION**" subsections, "UNCOATED AND FILM-COATED TABLETS," and "HARD CAPSULES" end the same way, "**assuming homogeneous distribution of the active ingredient**." Thus, when the **USP** permits homogeneity to be assumed, it is more important that the pre-release testing assure that the **USP**'s post-release condition is met than when the post-release **USP** testing requires a content uniformity determination.

Hopefully, the "scientific rationale for disallowing this exemption from the current draft guidance is" now unmistakably evident to the commenter.

Based on the preceding, hopefully, the commenter realizes that urging the Agency to include the requested exemption is not only unsupportable on its face but also could be broadly construed as a conspiracy upon the part of the industry to subvert the regulatory process.

In addition to the general comments, this commenter provided fourteen (14) pages of tabulated comments that this reviewer has evaluated.

To provide more space for the reviewer's observations and their basis, this reviewer merged the commenter's "Section" and "Guidance Line" columns and, because it is empty, has deleted the commenter's "Current Guidance Cross-Reference."

The tabulations containing the commenter's statements and the reviewer's remarks start on the next page.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
Numerous Places	We suggest replacing the word "correlation" with either the terms "relate" or "compare." From the context and the rationale, it is obvious that the commenter meant to say, "We suggest replacing the word '~~correlation~~correlate' with either the terms "relate" or "compare." Though this reviewer agrees in principle with what the commenter suggest, this reviewer recommends that the commenter's suggestion be modified to suggest that the use of all forms derived from the root "correlate" should be replaced with an appropriate alternative form from the root words "compare," "link" or "relate" except when a statistically valid comparative evaluation can be made.	The term "correlate" has statistical connotations. Because this guidance addresses scientific issues and the root word "correlate" has specific statistical connotations that are not appropriate in this context, wordings containing some form of the root "correlate" should be appropriately replaced as indicated, unless such statistical contrasts are being addressed.
General Comment	The guidance avoids the terms "validation" and/or "validation process," using titles like "verification of manufacturing criteria." We recommend including the terms "development" and "validation" to clarify the purpose of various sections." First, though the phrase "validation process" is not used, the word "validation" appears eight (8) times in the body of the Draft so it is less than fair to claim the guidance avoids the term "validation." Based on the commenter's recommendation, it would seem that the commenter's real concern is that the titles do not use the terms "development" and "validation" when, in light of the recent revisions to FDA **CPG 7132c** in **Sec. 490.100**, "Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08)," official as of 12 March 2004, this commenter should realize why the Agency avoided the use of the term "validation" in the titles of the sections in this drug product[1] guidance. Moreover, because this guidance is intended to apply generally, it is inappropriate to use the word "development" in the section titles because that word carries with it the connotation of an activity limited to new products when it is intended to be guidance applicable to all products. [1] **21 CFR 210/3(b)(4)**, "(4) Drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo."	The PQRI proposal makes it clear that certain activities should be performed during validation. The reluctance to use the term as a phase of development creates a disconnect with the PQRI proposal and makes the draft guidance more difficult to interpret. When addressing validation, the cited Agency CPG states (emphases added): "**Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110)**, and is considered an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs) under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. *A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product. The* ***proof of validation is obtained*** *through rational experimental design and the evaluation of data*, preferably **beginning *from* the process development phase** and **continuing *through* the commercial production phase.**" Based on the preceding, ALL such "drug product" batches are "validation" batches as per **21 CFR 211.110(a)**'s "control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that …" for each batch and its use to differentiate between phase would, *in light of this policy and the cited regulation*, therefore be futile. The basis for not including, the word "development" in the section titles is explicitly addressed in this reviewer's observations. Under **21 U.S.C. 321g(1)**, *that defines a drug*, all "development" batches that are administered to humans or animals are drug product batches upon which firms must use control procedures "to monitor and validate …" **21 CFR 211.110**.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
I. 18-23	The introduction should state that the limitations to current blend sampling procedures might preclude the effective use of blend sampling analysis to ensure the adequacy of blending and this guidance provides an alternate approach to assessing adequacy of mixing. This reviewer cannot support the commenter's suggestion because any limitations that "might preclude the effective use of blend sampling analysis to ensure the adequacy of blending" are limitations that the industry's failure to follow the precepts of sound sampling science and/or to develop mechanically stable blends inflicts upon itself. In addition, the alternate approach proposed does not assess the "adequacy of mixing" – at best, the alternate approach provides a biased non-representative sample estimate of the uniformity of the active and not, *as required by the in-process CGMP regulations for drug products*, a *batch-representative* assessment of the overall uniformity of the final blend (which this guidance persists in calling the blend though there are other pre-final-blend processing steps that, as the recent Pfizer article clearly shows, need to have their uniformity assured and appropriately controlled).	The key advantage of the guidance should be stated in the beginning of the document. The applicable CGMP regulation ***minimums*** governing in-process materials and the drug product clearly require a firm to assure the uniformity and integrity of each batch of drug product and clearly specify that such assurance shall include the monitoring the output and validating "the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product." (**21 CFR 211.110(a)**). In addition, **21 CFR 211.160(b)(2)** requires all in-process samples to be *representative* (as that term is defined in **21 CFR 210.3(b)(21)**), but the "stratified sampling" procedure proposed in the Draft, at best, does not ensure that the samples taken are batch representative samples nor, for that matter, does it sample sufficient samples for the assessment of all critical variable factors – not just *active uniformity* – that, *under **21 CFR 211.110***, must be assured. Moreover, the commenter's proposition clearly conflicts with the clear QCU evaluation and decision requirements set forth in **21 CFR 211.110(c)**.
I 18-20	We suggest providing a scope for powder blends to confirm that this guidance is applicable for critical blends of powders, granules, beads, etc. Since, as written, the draft guidance does not furnish *scientifically sound* and *appropriate* guidance that meets the CGMP ***minimums***, this reviewer cannot recommend that it be applied to any material as the commenter suggests. Based on the preceding reality, this reviewer suggests that the Agency revise this guidance so that it provides *scientifically sound* and *appropriate guidance* that conforms to the clear requirements of the CGMP regulations for in-process materials and the in process drug product.	Providing this scope will provide clarity of application users. Based on the 1988 US Supreme Court decision in *Berkovitz v. USA*, the Agency cannot legally issue guidance that is at odds with any clear binding FDA regulation. Since: a) this draft guidance is obviously at odds with the clear requirements of **21 CFR 211.160(b)(2)**, b) proposes sampling and evaluation plans that are neither ***scientifically sound*** nor ***representative*** of the *batch* (**21 CFR 211.160(b)**) and c) does not truly propose guidance that *assesses the uniformity of all the critical variable factors in each batch at each significant in-process phase when that factor **may** adversely affect the uniformity of the in-process materials and the drug product* (**21 CFR 211.110**), this guidance should not be finalized until it has been revised to conform to said requirement ***minimums***.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
III 60	We suggest revising line 60 to read: "Stratified Sampling of dosage units is the process of sampling at predefined intervals and collection… ." While this reviewer agrees that the commenter's suggested word order is more appropriate than that in the Draft, this reviewer cannot support the use of "***stratified sampling***" as defined by this guidance because: a. It does not require that the sampling points to be *representative* of the batch; b. the Draft proposes ***dynamic sampling*** (sampling while the dosage units are being formed), but does not require, *as it should*, that the samples at each sampling point must be ***representative*** *of* the *local variability at* the point in *time* where *each sample* is taken; and c. Does not require that the *number* of dosage units sampled should be more than the number required for ***batch-representative*** evaluations for all of the ***critical variable factors*** that **may** adversely affect the uniformity of the in-process materials and the in-process drug product. [**Note:** The drug product batch is an in-process drug product batch until the firm's QCU releases it for distribution.] This reviewer must therefore recommend that this draft guidance be revised until it conforms to the fundamentals of sound inspection science as they apply to the dynamic sampling of units from batches of units and conforms to the clear CGMP requirement **minimums** for the in-process materials and the drug product.	The term "stratified sampling" in italics implies a definition. The appropriate technical definition for stratified sampling is not limited to dosage units ; thus, the order of the words should be changed to comply with the PQRI proposal and definition. As per **21 CFR 211.160(b)(2)**, all in-process samples must be a ***representative sample*** of the batch of material as the term "***Representative sample***" is defined in **21 CFR 210.3(b)(21)** (emphases added), "***Representative sample*** *means* a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the ***sample*** *accurately portrays the material being sampled*," and, *as defined in this draft*, "**Stratified sampling**" does not meet the requirement **minimums** established in the CGMP regulations for drugs. For *dynamic sampling*, sound inspection science requires that each sampling point sampled must take a sample that is ***representative*** *of* the *local variability at the time of sampling* and this Draft does not even address this issue. The precepts of sound inspection science also require that the sample sampled should be of sufficient size (number) for all evaluations (of *all* the variable factors that should be evaluated, not just active content) that may be required since, for ***dynamic sampling***, it is not possible to go back (unless you have a time machine) and take additional samples at a sampling point. Since sound analytical science dictates that the sample sampled should be at least large enough for a test, a retest and a reserve (as Judge Wolin found in *USA v. Barr)*, the minimum number that must be sampled must be *at least* three (*3*) *times* the *number* required for ***all*** of the *variable factors* that must be assessed. In the CGMP regulations, "**Sec. 210.1** Status of current good manufacturing practice regulations" and "**Sec. 211.1** Scope" both clearly establish that the requirements in the CGMP regulations are the **minimum** – a firm cannot do less and comply.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
III 82-83	We suggest revising lines 82-83 to read as follows: "Compare the stratified in-process dosage unit data with the finished dosage unit data to determine whether in-process samples may be used to assess the uniformity of content."	Clarity
	Provided, **a)** this draft guidance is retitled and the text modified so that both unmistakably limit the guidance provided to assessing only one facet of the uniformity of the batch, active uniformity, and **b)** the non-representative by definition "stratified sampling" is replaced with *batch-representative* dynamic sampling defined using good inspection science in a CGMP-compliant manner, this reviewer would suggest the following language be used: "Compare the results obtained and their batch implications from the evaluation of an appropriate number of *batch-representative* dynamically sampled ~~stratified~~ in-process dosage units ~~data~~ with the corresponding data from the testing of a similarly appropriate number of batch-representative finished dosage units ~~data~~ to determine whether or not in-process samples may be used to assess the drug product batch's uniformity of content (for each active ingredient)."	Adherence to the precepts of sound inspection science and conformance to the clear applicable requirement ***minimums*** in the CGMP regulations. The phrase "uniformity of content" is also applicable to ingredients other than the active and the text should limit said phrase to the active unless it is evident to all that the guidance is restricted to assessing only the uniformity and integrity of the active(s) in the drug product. Until the guidance is retitled and rescoped to explicitly limit the guidance to ONLY the uniformity of the active or actives in any aspect of the manufacture of the drug product, this reviewer must suggest that the parenthetical phrase, "(for each active ingredient)", be included in the text.
III 95-96	Lines 95-96 should be revised to indicate that formulations with very high dose and or/low potency may require *less* rigorous sampling, not more rigorous sampling. This reviewer cannot agree with the commenter's suggestion for several reasons: 1. The Draft's current sampling is neither CGMP-compliant nor rigorous. 2. The commenter's proposal to revise not augment the present text to address the opposite condition is a fundamentally flawed postulation. 3. The current Draft does not sample an adequate number of *batch representative* units. Thus, this reviewer suggests that the Agency reject the commenter's obviously flawed suggestion.	Very high dose and/or low potency formulations tend to be less sensitive to differences in blend uniformity or less likely to result in patient subtherapeutic blood levels. Draft's sampling plans do not ensure that, *as required by CGMP*, the samples sampled are *batch representative*. With respect to dosage units, neither the number of samples that the Draft proposes to take nor the number of samples it proposes to evaluate is, in general, sufficient for a sound sample. Factually, "very high dose" formulations are mostly "extended release" formulations where the uniformity of the active within the release-controlling formulation matrix is often as sensitive (and, in some cases, more sensitive) to differences in the blend uniformity as many low dose formulations. Such "very high dose" formulations are more likely, through "dose dumping," to result in supertherapeutic "blood levels" that, in some cases, may be lethal to the patient.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
IV 108	For clarity, change the section title so that it clarifies that these exercises are Development (pre-validation) procedures. One possibility: "IV. Evaluating Powder Mix and In-Process Stratified Sampling During Process Development" Though this reviewer cannot agree with the commenter's suggested alternative, this reviewer does agree that this title should be revised. Based on the commenter's input, this reviewer suggest the title be changed to: "IV. **Establishing Sound In-process Active Uniformity Specifications For the Various In-Process Non-discrete Materials, Including the Final** ~~Evaluating~~ Powder Mix, and the **Discrete In-Process Dosage Units Produced Therefrom** ~~– Stratified Sampling During Process Development~~"	It is not clear (to all readers) that this section is a separate procedure from that proposed in Section V. A title and purpose statement will help clarify the reason for the differences in sampling scheme and lack of acceptance criteria. Properly, this section should address the issue of setting *scientifically sound* and *appropriate specifications* and *batch acceptance criteria* for each non-discrete in-process material and the in-process drug-product units produced by a given drug product process and not, as the commenter's suggested title indicates, activities that are exclusive to process development. Moreover, the title suggested by the reviewer clearly indicates that this section of the Draft addresses the setting of specifications for each active-containing in-process material (not just the final mixture from which the dosage units are formed) and the discrete in-process formed dosage units for active uniformity – one of several critical variable factors that must be appropriately controlled and evaluated in each in-process batch of drug product. Titled as this reviewer suggests, the purpose of this section should be clear to all.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
IV 115	We suggest revising line 115 to read: "through assessment of data from development batches." This reviewer does not agree with the commenter's suggestion and, *in keeping with the title this reviewer has proposed*, suggests that the text in Lines 111 – 119 be revised to read: "If you plan to follow the procedures described in this guidance document, we recommend that you first complete the ~~process~~ specification development procedures described in this section before using the methods described in sections V, VI, VII. The subsections below describe how to assess the adequacy of the various discrete in-process materials produced, including the final powder mix, the uniformity of the active content of the discrete in-process and finished dosage units through ~~correlation~~ comparison and assessment of data from development, validation and manufacturing batches. The purpose of these studies is to aid the manufacturer in establishing *scientifically sound* specifications for the uniformity of the active that appropriate for establishing *batch acceptance criteria* for each non-discrete, in-process material as well as for the discrete formed and finished dosage units in each batch. These ~~procedures~~ studies can reveal deficiencies in the blending operation that may not have been previously detected. We recommend that manufacturers correct all deficiencies in ~~the blending operation~~ their non-discrete material production steps before implementing the routine manufacturing control methods described in this guidance."	This section (Sec IV) is done prior to validation (per line 112), so reference to validation and manufacturing in line 115 is confusing. Since the confusion is introduced in Line 112, when the phrase "process development" is used when the phrase "specification development" is clearly the more appropriate, this reviewer has suggested correcting the Line 112. In keeping with the revised title suggested, this reviewer suggests modifying the rest of the paragraph in the manner suggested.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
IV-A 123	We suggest adding a "purpose statement" to this line. For example: "As part of development, we recommend that you assess critical events in the blend process and determine appropriate sampling techniques for demonstrating a validated blend process. As a part of this evaluation, we recommend the following procedures."	The suggestion adds clarity to help others understand the importance of this section.
	This reviewer does not agree with the commenter's suggestion because it falsely asserts that the reason for the added wording is "for demonstrating a validated blend process," something that, because validation is, *as the Agency clearly recognizes and the in-process CGMP regulations specify*, an ongoing "each batch" journey and not a destination, as the proposed text implies. Provided the guidance is restricted to the assessment of active uniformity, this reviewer offers the following alternative for the Agency's consideration: "As part of specification development, we recommend that you establish that each of your: **a)** Discrete-material sampling plans produces unbiased samples sufficient in amount for all evaluations and **b)** Test procedures appropriately samples and evaluates duplicate unbiased unit-dose, or smaller, sample aliquots from each sample so that you can thereby establish the validity of the results you obtain. As a part of these procedures, we recommend that you use the following procedures to assess the uniformity of each active in each non-discrete active-containing material produced by the drug-product manufacturing process you are evaluating."	**21 CFR 211.110(a) –** the clear "each batch" "monitor and validate" requirements contained therein clearly establish that validation is a journey and that no process that is being used can properly be considered to be validated – at best, such can be considered "valid" or "supporting the validity of the overall process." **See also**, the discussion on validation contained in Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08) of the FDA's Compliance Policy Guide 7132c effective 12 March 2004.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
IV.A. 125-126	We suggest adding a footnote to the end of this sentence *Sampling can be done from other equipment that is being used to mix the blend, such as a fluid bed. While this reviewer does not object to the footnote proposed, this reviewer knows that the alternative suggested belongs in the text and suggests the following alternative for **Lines 125-126**: "• Conduct blend analysis on batches by extensively sampling from the mix in the blender or other equipment used to produce the mix (e.g., the fluid bed in a fluid-bed blender) and/or from the intermediate bulk containers (IBCs) into which the non-discrete materials are transferred*." * The degree of agreement between the results from the samples from the production vessel and those from the IBCs is a measure of the short-term mechanical transfer stability of each active-containing mixed material that the drug-product process manufactures before the final such material is converted into the formed dosage units. In general, firms should evaluate this mechanical transfer stability.	Clarification is needed to insure that the guidance can also be used with non-traditional processing equipment. In early development, sampling from the mix, blend, or fusion container at the completion of a processing is often the only or better choice because the equipment itself is small, easily sampled, and often the intermediate storage container (IBC). As development proceeds and batch volume increases, there comes a point at which a batch-representative set of unbiased location representative samples that are each sufficient in amount to permit the sampling of a number of unbiased dosage-unit-sized aliquots (that number should be at least three times the amount required for all possible evaluations for all critical variable factors, including the active or actives) cannot be collected and the sampling plan should shift the sampling point to the IBCs (and, in some cases, the material remaining in the container in which it was produced) and sample the requisite batch-representative set of unbiased location-representative samples from the IBCs. When the samples sampled are tested, in general, duplicate aliquots should be evaluated to ensure that the within-location variance can be properly estimated and to guard against an undetected analytical error.
IV.A.	We suggest changing "Sample Size" to "Sample Quantity" While this reviewer agrees with the commenter that "Sample Size" is an inexact term with multiple meanings that should be replaced, but he suggests that the appropriate replacement phrase to use is "Sample Amount"	Clarity as sample size relates to a volume measurement. In inspection science, the term "sample size has two meanings, "number or amount" For the non-discrete materials, the word "amount" is the appropriate choice. Moreover, the word "quantity" carries the connotation of a "number" choice, which is clearly inappropriate here.
IV – A 137 & 140	We suggest changing the word "Significant" to "High" in both lines. This reviewer rejects this obviously wrongheaded suggestion. Since the texts in question are discussing statistical measures (*within-location variance* and *between-location variance*, respectively), the word "Significant" is obviously the appropriate word to use.	Because the term "significant" may imply "statistical significance." The change would avoid confusion and comply with PQRI terminology. When the texts are clearly discussing a statistical measurement (variance) the change suggested is inappropriate whether, or not, it meshes with the PQRI terminology. For *variance*, tests of "statistical significance" are exactly what should be used.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
IV.A. 138-139	We suggest adding to this section that within-location variance may also indicate analytical errors. This reviewer cannot support the commenter's suggestion because it is a tangential reality that only detracts from the guidance being provided. All variances in results obtained by the analysis of samples include an analytical variance (analytical error) component.	This is another factor that may produce within location variance. Between-location variance also contains an analytical-error variance component. Hopefully, the firm's laboratory controls are adequate to: **a.** Ensure that, in general, such errors are minimal net contributors to any overall variance for a set of sample results and **b.** Detect almost all instances where the analytical-error component to a given variance is the major component and take the appropriate action. Failing that, hopefully the firm will detect their lab's incompetence and take the appropriate corrective actions.
IV-B 146	We suggest adding a "purpose" statement to this line. For example: "Prior to validation, we recommended that you assess the in-process dosage units data to identify locations throughout the compression/filling operation that have a higher risk of producing failing finished product uniformity of content results and to identify trends due to segregation or poor powder mix. We recommend the following steps." Though this reviewer has no objection to adding a "purpose" statement, this reviewer finds the commenter's suggested text at odds with the principles of validation and unrealistic. Until the flawed guidance offered is corrected in a manner that fully conforms to the applicable requirement ***minimums*** of the CGMP regulations this reviewer cannot recommend appropriate wording. However, this reviewer notes the following problem areas that should be addressed by the Agency: 1. The multi-level analysis of the final blend material in the IBCs used to charge the feed to the dosage forming equipment 2. Sampling a *representative number* of units from each dosage-forming station at each sampling point. 3. Evaluation of a *representative set from each sample sampled* from the in-process formed dosage units. 4. Linking the uniformity of the material in each IBC to the uniformity of the dosage units formed from it, 5. Restricting the guidance to the uniformity of the active or actives present.	Adding a purpose statement would help others understand the importance of this section. Since most recognize that validation begins in development and labels that phase as the Design/Development Qualification phase (DQ), the actions suggested here fall within the validation envelope. Unless the guidance provides some mechanism (like the one suggested) to link the results from the some part of the final blend to the results for the dosage units produced therefrom, there is no way to effect the identifications suggested. Even when the guidance is restricted to the uniformity of the active or actives, measuring active level does not address or ensure overall uniformity. Because dynamic sampling is the sampling used, the failure to require the taking of at least one unit from each dosage –unit-forming station at sampling point fails to ensure that the samples sampled are *representative* of the *batch*. Under the present scenario, all that can be compared is an uncertain final blend's active uniformity based on biased samples to a non-representative-sample-based even less certain estimate of the active uniformity in the formed dosage units tested. Under the Draft's scenario, the weight-corrected active content values computed from the biased dosage results only provide biased estimates of the variance of the blend plus variance of the transfer operations, the variance introduced by the dosage-unit-forming process, and the lumped error variance.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
IV – B 160-161	We suggest changing lines 160-161 to read: "Prepare a summary of the data (and analysis), identifying the significant events in the manufacturing process that may impact blending and from this, identify the stratified sampling that may be used to verify powder mix uniformity. We… ." This reviewer does not support the commenter's suggested wording for the cited text for the same reasons as he stated previously. Provided the draft is restricted to only assessing the uniformity of the active or actives and the text is modified to require the in-process dosage units evaluated to be not less than 200 batch-representative units composed of the results for an equal number, chosen at random, from each routine sampling point and any additional sampling points, this reviewer suggests the following alternative: "• Prepare a summary of the data including the weight-corrected content values for each tablet tested and the corresponding statistical estimates derived therefrom, minimally at the 95-% confidence level, and compare those statistical estimates to the corresponding statistical estimates for the active level in the final blends." 8. Compare the blend results from each IBC to the weight-corrected results from the tablets linked to the IBC. 9. Compare the statistical estimates of the batch result limits for the blend to those from the in-process dosage units. 10. Enter all results into an appropriately constructed table. 11. Use the appropriate statistical analysis procedures and a confidence level of not less than 95 % to analyze all the data and generate appropriate findings as to the predicted active uniformity of the blend and the in-process dosage units as well as the relationship, if any between IBC results and the related dosage units. 12. Report all data and findings. [**Note:** If the active's variance for the in-process dosage units is significantly larger than that for the blend, investigate and, once the cause has been found, take corrective action.]	This change would help clarify purpose and prevent some confusion over the statistical use of the term (correlate." Comparing biased estimates of the blend's active uniformity from a few singlicate (ca. 20) non-representative blend results with no local estimate of result reproducibility to the in-process dosage-units' active uniformity from a few (ca. 140) non-representative dosage-units' results that are, at best, weakly linkable as in the Draft's scenario is a less than scientific procedure. If the guidance is restricted to the active(s), in development the guidance should direct: 1. Sample a *batch-representative* number of unbiased samples from multiple levels in each of the IBCs of the final blend coupled and perform duplicate aliquot evaluations (with at least two measurements on of the active in each aliquot) on each sample from each IBC in a manner that links the results to the location in the IBC location from which it came. 2. *At not less than 20 sampling points across the production of formed dosage units*, take not less than four (4) dosage units for each dosage-unit-forming station *at each sampling point, "routine"* ("start," "n time point," and "end") and "*significant event"* (e.g., restart, hopper rundown), and collect each in a separate, appropriately labeled container, 3. *At each sampling point*, note the IBC container number and approximate level of the blend that is being formed until all samples have been collected. 4. *From each "routine sample" sampling point container*, take not less than ten (10) dosage units chosen at random from that sampling point and label the test-sample container with its sampling point ID. 5. *From each "significant event" sampling point container*, take not less than ten (10) dosage units chosen at random from that such sampling point and label the test-sample container with its sampling point ID 6. Weigh and analyze all samples in a manner that provides at least two valid measurements for each dosage unit and preserve all result, ID and weight links 7. Compute the "as is" and weight-corrected active level for all active level results. (← Continues in the adjacent column)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
IV - B 163-164	We suggest changing "data described above" to "uniformity." This reviewer <u>cannot</u> support the change suggested. At best, the Draft's "in-process dosage-unit data described above" can only be validly described as the "active's uniformity." <u>Provided</u> the sampling procedures are corrected to ensure that an appropriate number of batch-representative samples are evaluated in each case, based on the preceding factual reality, this reviewer recommends that the text in Lines 163-164 be revised to read: "• Compare the powder mix uniformity statistics-derived results for the active or actives (obtained using the approaches outlined in Subsection A) with the corresponding in-process dosage-unit statistical population inferential values for the uniformity of the active(s) derived from the weight-corrected response result values obtained using the procedures described in this section. ~~data described above~~."	The change would provide clarity when comparing powder mix uniformity to the dosage unit uniformity. Since all that this draft guidance measures is the level of the active or actives in each sample, use of the term "uniformity" must be restricted to the active(s) (e.g., "uniformity of the active(s))." Moreover, because neither of the procedures proposed in the Draft take and evaluate samples that are representative of the batch, a more appropriate phrase would be "biased estimate of the uniformity of the active(s) in the final blend/in-process formed dosage units" As was the case in the previous section, the Draft's guidance is at odds with applicable CGMP regulations and needs to be revised in a manner that renders the revised text fully compliant with the applicable CGMP requirement ***minimums***.
IV - C 172	We suggest changing this section title to: "Establish the relationship between stratified in-process samples and the finished product" This reviewer does <u>not</u> support the commenter's suggested change and notes that the change proposed here is even at odds with the commenter's first suggestion (in the row labeled "Numerous Places"). <u>Provided</u> the sampling and the sample evaluation plans are changed to specify that all must be *representative* and the guidance is restricted to the active or actives, this reviewer would recommend changing the cited title to: "Comparison Of the Uniformity Of the Active(s) In Dynamically Sampled In-Process Dosage Units To the Uniformity Of the Active(s) In the Finished Product"	Because "correlate" has statistical connotations, changing the title would help clarify its intent. Since the Draft, as written, does <u>not</u> even sample, or evaluate sufficient (in number) *batch-representative samples* to establish, with a high degree of confidence (95 % or higher), unbiased estimates of the uniformity of the active (or actives) in either the freshly formed in-process dosage units or final in-process drug-product dosage units, the current Draft only validly permits you to crudely "compare" the two (2) estimates of the uniformity of the active or actives. Furthermore, the current guidance is clearly at odds with the applicable CGMP regulations and must be corrected until it fully conforms to the requirement minimums established in said CGMP regulations. Finally, until a body (≥ 15) of production-scale batches has been accumulated over a significant time period (≥ 1 years), all that you should do is ***compare*** the uniformities observed for the two dosage-form phases – proving the overall relationship requires a significant body of evidence.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
IV - C 172-185	We suggest that FDA move this section under topic of Section VI, with the additional option that if this verification has previously been completed in development, it is not necessary to repeat the evaluation. This reviewer cannot agree with the commenter's suggestion here as it flies in the face of both common sense and sound science. If you cannot find in development, or at any other point in time, that the uniformity of the active content in the freshly formed dosage units is comparable to the uniformity of the active in the finished dosage units in all the development-related batches, either the process in question falls outside the scope of this guidance (e.g., more of the active is added in one or more coating steps) or, *if the drug product definitely falls within the scope of this guidance for assessing the uniformity of the active*, your product development activities have, to date, been inadequate. Moreover, the guidance furnished in the Draft clearly conflicts with many of the requirements set forth in **21 CFR 211**. Therefore, this reviewer again strongly suggests that this section of the guidance be revised until it conforms to all of the applicable requirement minimums set forth in the CGMP regulations.	Many companies will use the extended testing during validation to compare in-process to finished product, in order to obtain better estimates. During development, it may not be practical to obtain a sufficient amount of data to demonstrate equivalency or "correlation" between the final and the in-process product. It should be obvious that a drug-product falling within the true scope of this guidance (*assessing the uniformity of the active or actives in the in-process materials and the drug product [a single-layer, single fill tablet or capsule made from a single uniform final blend]*) must have an active uniformity in the freshly formed dosage units that is comparable to the active uniformity on the finished dosage units tested for release for distribution (for each active) or the process development needs to be continued or restarted. However, the guidance in this section does need significant revision to ensure that sufficient *batch-representative* drug-product samples are appropriately evaluated against *scientifically sound* and *appropriate batch specifications* and *acceptance criteria* which ensure that all of the untested units in the batch will, after the batch is released, meet the **USP**'s "in commerce" requirements. If the uniformity of the active is the only aspect of the assessment of the uniformity of the drug product, the minimum number of drug-product samples that must be tested is on the order of 200 (the minimum number that should be tested is on the order 200 to 900 *representative* units depending upon the level of confidence required for setting process' projected limits and initial specifications). The *scientifically sound* and *appropriate acceptance criteria* should include those established for the batch in the recognized consensus standards for the inspection of variable factor for the percent nonconforming published by ANSI and ISO. This is the case for drug products because, *for release*, the drug product dosage units must meet the requirements set forth in **21 CFR 211.165(d)**.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
IV - C 174	We suggest changing the sentence to: "We recommend the following steps to support the use of stratified in-process sample data as an alternative to the USP Content Uniformity Test:" Given all of the clear divergences in the commenter's suggested text from the unambiguous ***minimums*** established by the applicable CGMP regulations, this reviewer cannot support the commenter's suggestion. This reviewer suggests the following alternative: "We recommend the following steps to support the use of ~~stratified~~ the in-process ~~sample data~~ inspection as an alternative to the ~~USP Content Uniformity Test~~ drug-product release testing required by **21 CFR 211.165(d)**:" --- **Note:** With respect to the commenter's statement "the results from the stratified samples would be harder to pass since it would be more likely to include outliers," this reviewer notes: 1. A valid evaluation of any set of samples cannot find units that have active levels that are not present in any sample from a batch that is so assessed 2. For sample sets of the number (140) specified in "stratified sampling" for the development of specifications, where the expectation should be that almost all of the samples will have active results that are within "3 times the batch estimate of the active content's RSD. 3. Given the **USP**'s post-release active content expectation of "85 % to 115 % of target" and the absolute limits of "75 % to 125 % of target and the recognized properties of distributions of all kinds, the commenter's statement here indicates that the commenter seems to know that some significant percentage of the current drug product batches released evidently are **drug product batches that have more than 3 failing units in a 1,000** that have active content's that are either less than 75 % of target or greater than 125 % of target while **today's CGMP expectation vis-à-vis active uniformity is** a rate that is close to **3 units in 1,000,000 or less**. [Hopefully, the Agency has also appropriate noticed this.]	Because content uniformity testing of the stratified in-process samples is more rigorous that that for the USP Content Uniformity test the results from the stratified samples would be harder to pass since it would be more likely to include outliers. The CGMP regulations (**21 CFR 211.160(b)(2)**) clearly require that all in-process samples evaluated must be *batch representative* and, as defined in the draft guidance, "stratified sampling" does not ensure that truly *batch-representative samples* are taken or evaluated. The CGMP regulations (**21 CFR 211.160(b)(3)**) also require that all drug-product samples evaluated must be *batch-representative* and, as the **USP** notes, the **USP**'s sampling plan does not take samples that are *batch representative* Moreover, the sample numbers in the **USP** (30) are not sufficient to meet the minimum number requirements (75 [for batches between 3200 and 10,000 units] to 200 [for batches larger than 150,000) for the "process variability unknown-SD," "normal inspection" case (*which is the case during development*) in the applicable recognized consensus "acceptance level" (AQL) standards published by ANSI and ISO. **21 CFR 211.165(d)** requires each batch to meet "… and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include **appropriate acceptance levels** and/or appropriate rejection levels." Thus, the recognized consensus standards, ANSI Z1.9 or ISO 3951 are applicable recognized consensus standards that, *at the 95 % confidence level*, should be used to set the effective minimum number of batch-representative samples that must be evaluated to comply with the clear requirements set forth in **21 CFR 211.1265(d)** for drug-product evaluation for release.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
IV - C 186	We suggest adding another bullet point: "If the in-process samples cannot be used to assure the uniformity of dosage units, then the compendial test on the final product will need to be continued in addition to in-process stratified testing for blend uniformity." This reviewer supports adding another bullet point. However, as the reviewer's remarks in the previous row clearly support, the text proposed is clearly at odds with CGMP and should not be used as the basis for that bullet point. Instead, this reviewer proposes adding the following CGMP-compliant bullet point: "If the active content results for the in-process samples tested using the appropriate 'process variability unknown-SD,' 'normal' inspection plan in ISO 3951 or ANSI Z1.9 indicates that the batch fails to be sufficiently uniform, then, unless the sample results are all inside of the **USP**'s post-release requirements of "75 % to 125 % of target," the batch under test should be rejected and an investigation that has the goal of finding the root cause(s) and implementing the requisite root-cause-corrective actions should be started. In cases where the batch acceptance quality level is not met but all values are inside of the **USP**'s any-unit limits, then, after initiating a root-cause investigation, an appropriate augmenting set of *batch-representative* sample units (typically the same number as required for the full initial test) may be tested and the results evaluated using a distribution-free approach to assess the batch's acceptability provided the firm's inspection plan are hierarchical in nature and explicitly provide for this option. Otherwise, such developmental batches must be rejected."	The bullet provides guidance and flexibility if a relationship cannot be established at that time. First, all of the reviewer's applicable prior remarks concerning what is required for acceptable uniformity for the active or actives in the in-process dosage units (whether they are freshly formed or finished dosage units) are incorporated by reference. Nowhere in the CGMP regulations governing all aspects of the drug product's production do the regulations permit the in-process evaluation of non-representative materials or drug product units. . The **USP**'s sample and test plans only apply to post-release materials in commerce – they do not apply to in-process materials and in-process drug product. As the **USP** clearly states, the **USP**'s sampling plans are not statistical sampling plans (statistical sampling plans are a prerequisite for a representative sample) and the USP's specification limits can only be directly applied to the **USP** "article" after the batch is released. *Based on the preceding*, under CGMP you cannot be complying with the applicable CGMP regulation ***minimums*** if you are directly using the **USP**'s post-release inspection plan and acceptance criteria for releasing batches of in-process dosage units and/or the drug product in the development phase. [**Note:** The only possible exception to the preceding would require the entire batch to consist of 500 dosage units or less – but even here the acceptance criteria would have to be appropriately inside of any limits range or inside of any single limit specification because you are only testing a small percentage (6 % for a 500 dosage-unit batch) of the batch. Given the size constraints on tablets and capsules that patients can swallow, s 500-unit batch translates into a 0.5 kg or smaller batch size and, in my experience, the typical least-size batch is on the order of 2 kg (or ≥ 2,000 units).]
V. 188	Validation" is misspelled. This reviewer agrees.	
193-196	We suggest changing this paragraph to: "In order to establish uniformity of blend during validation and/or exhibit batches, we recommend an assessment of both powder blend uniformity and in-process dosage unit uniformity. We recommend you use the following steps to identify sampling locations and acceptance criteria should be identified prior to the manufacture of these batches. (insert footnote 15 here)" (Continued on next page)	The PQRI BUWG recommendation states both blend and dosage unit evaluations are needed to establish uniformity. This also clarifies footnote 15. Unfortunately, those who fashioned the PQRI BUWG recommendation seemed to ignore many of the precepts of inspection science, the existing consensus standards that apply to the assessment of the uniformity of discrete units, and some of the clear CGMP regulations that without a doubt apply (continued on the next page)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
193-196 (Continued)	(Continued) While this reviewer agrees with the commenter that the text needs to be modified to improve its readability, the reviewer cannot accept the commenter's suggested revisions to the text. This is the case because the commenter's proposal fails to meet the applicable "to monitor the output and to validate …" in-process requirements for each batch of the drug product as set forth in **21 CFR 211.110**,governing the "Sampling and testing of in-process materials and drug products." Provided the scope of the draft guidance is explicitly restricted to "*assessing the uniformity of the active or actives in the drug product for each batch*" instead of the present misleading "assessing the uniformity of the drug product for each batch," this reviewer recommends that the text be revised to read as follows: "In order to establish **batch** uniformity of **the active or actives in** ~~the~~ **each mix or** blend**, the in-process formed dosage units and the in-process finished dosage units** during ~~validation and/or exhibit~~ **the production of each conformance** ~~batches~~ **batch,** we recommend an assessment of ~~both~~ **the uniformity of the active in each active-containing mix, including the final** powder blend**,** uniformity **the final blend in IBCs, the** in-process dosage unit**s, and the finished dosage units using unbiased *batch-representative* sampling and sample assessment** ~~uniformity~~**. We recommend that, when the batch exists as a collection of discrete units, you should use the appropriate (for batch size) "process variability unknown," normal inspection plan in ISO 3951 as the basis for your sampling plan. We recommend that you choose the AQL (% nonconforming) that is appropriate for the size of your batch and the quality of your process for determining the batch acceptance criteria for your inspection plan. Further, we recommend that you justify the narrowing of your expected range of active levels inside of the USP's expected values range in terms of your targeted quality level (expressed in the allowable RSDs about the target active content) and your risk of accepting a batch that fails to meet the range you set.** (Continued on the next page)	(Continued) to *each batch* of in-process material and drug product. The use of the phrase "**conformance batch**" is suggested because it is the terminology that the Agency adopted in its recent (12 march 2004) its revision to **Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08)** which contains the pertinent text (**bolding** added): "Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110), and is considered an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs) under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product. The proof of validation is obtained through rational experimental design and the evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase. … Before commercial distribution begins, a manufacturer is expected to have accumulated enough data and knowledge about the commercial production process to support post-approval product distribution. Normally, this is achieved after satisfactory product and process development, scale-up studies, equipment and system qualification, and the successful completion of the **initial conformance batches**. **Conformance batches (sometimes referred to as "validation" batches and demonstration batches)** are prepared to demonstrate that, under normal conditions and defined ranges of operating parameters, the commercial scale process appears to make acceptable product. Prior to the manufacture of the **conformance batches** the manufacturer should have identified and controlled all critical sources of variability. (Continued on the next page)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
193-196 (Continued)	(Continued) We recommend you use the following steps to identify sampling locations **for sampling from non-discrete materials and the statically sampled finished dosage units, sampling points for the dynamically sampled in-process discrete units, amount to sample from each non-discrete material location**, **number to sample at each discrete-material location, number to sample at each sampling point,** and **the** acceptance criteria **for each in-process active-containing non-discrete material produced and each production step that produces a batch of discrete units (typically, the formed dosage units and the finished dosage units)**. [**Note:** These should be identified prior to the manufacture of these **conformance** batches.[15]] [15] This is described in Section IV of this guidance."	(Continued) As the recent Pfizer article in the March 2004 issue of Pharmaceutical Technology demonstrates and the applicable CGMP regulations governing in-process materials and drug products require, if your process includes an active-containing preblend or intermediate blend or granulation, you must include the evaluation of the product from each manufacturing phase in addition to the final blend. [**Note:** One of the fundamental precepts of the cost of quality is that the sooner you find the problem in a multi-step process, the lower the costs to correct the problem and the greater the probability that you can identify the true root cause(s) of the problem and take effective corrective action that minimize the risks of a recurrence.] If you wish to compare the results obtained from the weight-corrected active values obtained from the formed dosage-units evaluated at each sampling point to the corresponding part of the final blend used to manufacture the said units, then you must obviously collect the final blend samples from the IBCs used to contain the final blend in a manner that truly links those results.
197	Please consider moving the last 2 paragraphs (Line 224 through 233) before sampling specifics starting in line 198. This reviewer agrees that the last two paragraphs need to be moved <u>but</u> disagrees with the placement suggested by this commenter. This reviewer suggests that these be <u>removed</u> from the draft guidance because the specific "safety" and other more nebulous justifications offered here and in the draft are but the last red herrings offered by those who seek to evade compliance with the clear requirements of the CGMP regulations concerning the inspection required for each batch at the start or completion of each significant phase in the drug product manufacturing process. If the Agency truly believes that quality should be built into each drug manufacturing process, then, *given today's lack of rigorous controls on all of the critical physical properties of each component*, appropriate monitoring of each critical variable factor, or its surrogate, at each significant phase in the production of each batch of product, as the CGMP regulations clearly require, should be required and enforced for all drug products.	Moving these paragraphs provides background acknowledging that blend sampling may not be appropriate if demonstrated in product development. Given the wide availability of Class 4 material isolators and robotic samplers, there are no insurmountable safety issues. The sampling bias and sampling difficulty issues are based on <u>false premises</u>, including, *but not limited to*: • Biased sampling is required or even acceptable. • The law does <u>not</u> permit the sampling of unbiased multiple-dose samples for active uniformity assessment. • Samples sampled from non-discrete materials do <u>not</u> have to be large enough in amount for all of the required testing for each variable factor that may adversely affect the uniformity or quality of the in-process materials or the drug product. The Agency and the Industry seem to forget that it is incumbent upon the drug product industry to develop rugged uniform (for all critical factors and <u>not</u> just the active level in the final blend) final blends that are more than adequately uniform (exceed the CGMP minimums), and easily sampled (and therefore strongly resistant to post-blending resegregation and stratification).

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
198	We suggest rewording this section to read as follows: "1. Identify at least 10 locations to collect powder blend samples. If taken from the blender, they should include areas that may be problematic in terms of uniform blend." This reviewer finds the commenter's rationale is flawed and specious. Considering the fundamentals of sound inspection science and the requirements of the CGMP regulations that clearly require the inspection of each batch of each distinct in-process material produced during the production of the drug product, this reviewer proposes the following alternative for the steps in the draft provided that draft is restricted to the assessment of the uniformity of the active(s) in each batch of drug product: "1. *For each distinct in-process non-discrete "powder" product produced (e.g., mix, blend, fusion)*, select that minimum set of post-production locations that development has proven to be representative of the uniformity of the active or actives in the material being sampled. In general, when sampling the materials as a whole from a *conformance batch*, that set should consist of not less than (NLT) 15 locations and, when sampling from a set of NLT 5 IBCs, that set should consist of NLT 1 sample from the top, middle, and bottom of each IBC. The sampling plan used must span the batch and, *for the material as a whole*, appropriately include at least one sample from a location that previous studies and information have proven to represent, on average, the "least uniform" material as well as one from the corresponding similarly proven to represent the "most uniform" material location. 3. *From each of the representative sample locations identified*, use a proven unbiased sampling and sample handling procedure to collect an amount of material that is adequate to provide an unbiased sample that is at least three times the amount needed for the evaluation of all of the critical variable factors in the material, including the active or actives. Place each unbiased *location-representative sample* into a properly labeled container that is sized so that the sample fills the container, close the sample container, and place it upright in a suitable transport carrier. (Continued on page)	The suggested change provides background acknowledging that blend sampling may not be appropriate if demonstrated in product development. The CGMP regulations require all "specifications, standards, sampling plans, and test procedures ***designed to assur***e that components, drug product containers, closures, **in-process materials**, labeling, and ***drug products conform to appropriate standards*** of identity, strength, quality, and purity," **to be *scientifically sound*** and ***appropriate***. (**21 CFR 211.160(b)**) The CGMP regulations require all in-process samples to be *representative* (**21 CFR 211.160(b)(2)**) as the phrase "representative sample" is defined in **21 CFR 210.3(b)(21)**, "**Representative sample** *means* a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled." The CGMP regulations require sampling and evaluation of all critical variable factors, or their surrogates, in each batch of each material produced in each significant phase of the manufacture of the drug product including the in-process finished drug product (the stage at which the drug product is ready for evaluation for release) as follows: 1. **21 CFR 211.110(a)**, "**To assure batch uniformity and integrity of drug products**, written **procedures shall be established and followed that describe** the **in-process controls, and tests, or examinations to be conducted on** appropriate **samples of in-process materials of each batch**. Such control **procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product**. Such control procedures shall include, *but are not limited to*, the following, where appropriate: **(1) Tablet or capsule weight variation**; (2) Disintegration time; **(3) Adequacy of mixing to assure uniformity and homogeneity**; **(4) Dissolution time and rate**; (5) Clarity, completeness, or pH of solutions." 2. **21 CFR 211.110(c)**, " **In-process materials shall be tested for identity**, **strength**, **quality**, and **purity** as appropriate, **and approved** or rejected **by** the **quality control unit**, **during the production process**, **e.g.,** at commencement or **completion of significant phases** or after storage for long periods." (Continued on page)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
198 (Continued)	(Continued) 4. *After collecting all of the required location-representative samples required to generate a batch-representative sample (as required by **21 CFR 211.160(b)(2)**)*, transport said *batch-representative sample* to where it will be evaluated. 5. *At the evaluation location*, carefully remove two (2) unbiased approximately *unit-dose aliquots* from each sample sampled and prepare them for analysis. Retain the samples sampled for use in the evaluation of other critical variable factors. When the entire set has been prepared, randomize the evaluation order of the prepared samples and along with the appropriate standard preparations evaluate the samples in a manner that the results consist of two or more measurements (or a valid instrument-averaged equivalent) of each sample-aliquot preparation. 6. Appropriately analyze the valid results obtained against the *scientifically sound sample specifications* established during development as well as the appropriate *batch acceptance criteria* derived from the sample results found. 7. Have your QCU determine whether or not the samples tested meet the specifications established and predict that the batch has an acceptable level of uniformity for all actives present in the material being evaluated. 8. When the material is acceptable, the QCU should accept the final blend for release for use in the next production step pending the completion of all other variable assessments; if the QCU cannot accept it for release, quarantine it appropriately and initiate an investigation to determine the root cause(s) for the failure and the corrective action, if any, that has a high degree of certainty of bringing the material up to expectation, and, after QCU approval, proceed as your QCU directs. 9. Incorporate all findings into the Process Performance Evaluation that should be an integral part of the initial conformance assessment for the drug product. In general, you must establish the validity of all your *sample specifications* and derived *batch acceptance criteria* for active uniformity, and, except for the last non-discrete material, no general prescriptive guidance has been suggested for these.	(Continued) 3. **21 CFR 211.110(b)**, "**Valid in-process specifications for such characteristics shall be consistent** with drug product final specifications and shall be **derived from previous acceptable process average and process variability estimates** where possible **and determined by the application of suitable statistical procedures** where appropriate. **Examination and testing of samples shall assure that the drug product and in-process material conform to specifications**. 4. **21 CFR 211.110(d)**, "**Rejected in-process materials shall be** identified and **controlled under a quarantine system** designed to prevent their use in manufacturing or processing operations for which they are unsuitable." The published apparently *scientifically sound* evidence including a recent Pfizer-released article in the March 2004 issue of **Pharmaceutical Technology** (**24**. **No. 2**, pages 110, 112, 1114, 116, 118, 120-122) by T. P. Garcia, A Carella, and V. Panza, "Identification Of Factors Decreasing the Homogeneity of Blend and Tablet Uniformity", the need for the CGMP-mandated inspection and control of the uniformity of materials produced prior to the "final mix" has been established. *Based on that reality*, it is clear that, *even if the guidance is limited to assessing one aspect of the drug product's critical uniformity factors, active uniformity*, the guidance should explicitly include guidance that addresses such in-process production materials. *As the article clearly found*, improving and controlling the uniformity of the active in a "Preblend" was key to establishing an apparently appropriate uniformity for the active in the final tablets, even though the blend means clearly seemed to indicate that the sampling procedures used produced biased samples and, therefore, should be improved.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
198 (Continued)	(Continued) For the "final" non-discrete material used to manufacture the formed dosage units, all of the *sample specifications* and derived *batch acceptance criteria* for active uniformity cannot be prescriptively set because the appropriate values for these depend upon the post-phase variance contributions contributed by material handling and the dosage forming system itself. However, the following criteria should be met: 1. All the "unit dose" samples evaluated should be expected to have valid active result mean values that are within "90% to 110% of the target drug-product active level." 2. The sum of: **a)** the results' relative variance, **b)** the maximum post-step relative variance (established during development) and **c)** the maximum dosage-forming relative variance (found during development) should be not more than 9.0 $\%^2$. 3. The average for the *batch-representative samples* tested must be NLT 100 % of the label claim unless the production process provides for a small correction (≤ 1%) in the formed dosage's targeted running weight (in which cases, the observed mean should be not less than 99 % of the label claim. 4. The average within-location variance should be less than or the same as the overall between-location variance. 5. The "within-location" variance for the "proven worst" location should be larger than the variance found for the "proven best" location. 6. At the 95%-confidence level, the predicted limits for the active level in the blend should be appropriately inside of the range from "85.0 % to 115. % of the targeted level"	

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
V Amendment Line number 216 (new text)	We recommend the following change to this paragraph: "If samples do not meet these criteria, we recommend that you investigate the failure according to the flowchart in Attachment 1 by assaying the remaining replicate blend samples and at least 7 dosage units from each in-process sampling location. Identify the root cause of the failure. If the root cause is a mixing problem, we recommend that you proceed no further with implementation of the methods described in this guidance until you develop a new mixing procedure. If the cause of the failure is attributed to sampling, assay, or another problem unrelated to homogeneity, we recommend that you use the methods in Attachment 1 and Section VI (Verification of Manufacturing Criteria) to determine the adequacy of mix. We also recommend that if you cannot identify the cause of the failing criteria that you do not proceed any further with implementation of the methods described in this guidance." Because the CGMP regulations clearly require "*final blend" inspection* and *release* by the QCU prior to the initiation of dosage formation and direct that *failing in-process materials must be quarantined* and withheld from use until an investigation can determine they are suitable for the step in which they are to be used, this reviewer cannot support the guidance provided here. In addition, the suggested course of action is at odds with the fundamental precepts of the "cost of quality" that counsel investigation and "root cause" incident corrective/ongoing preventive actions before you proceed with the manufacturing process. In addition, this reviewer cannot support the guidance proposed because, as published, it does not take a *batch-representative set* of *unbiased samples* of an amount in excess of three times the amount needed for the evaluation, in duplicate, of all of the critical variable factors in the final blend and evaluating unbiased duplicate aliquots from each sample for the level of active(s) in each sample sampled. *Until this guidance's fundamentally flawed approach to blend sampling and blend-sample evaluation is corrected*, this reviewer sees no value in commenting further about the Draft's present sampling plan or the equally flawed scheme associated with it.	At the December 2003 PQRI workshop, it was identified that the flowchart 1 is slightly incorrect. This change would address the situation if blend samples do not pass stage 1, dosage units are assayed to help identify blending sample error, prior to deciding if sample error is present. First, this reviewer finds that the commenter's stated rationale has little to do with the text other than to again state that its "OK" to use a failing blend to make tablets when making a process conformance batch – a point in the validation of your process where this reviewer and the FDA, in Section 490.100 CPG7132c.08 (effective on 12 March 2004, expect that you have already "**identified and controlled all critical sources of variability**." Thus, if you have truly identified and controlled all critical sources of variability, this reviewer, the Agency, and other scientists who understand the development of drug-product processes for tablets and capsules expect that failures of the valid active content blend results to meet *any* of the blend's ***scientifically sound*** and ***appropriate sample*** *specifications* and *batch acceptance criteria* should be rare. Sound inspection science for non-discrete materials dictates that each sample must be an unbiased sample that is larger than the amount required for a full test, retest and reserve for all of the critical variable factors (chemical and physical) that should be evaluated. In addition, *for batch-representative sampling*, the sample locations chosen must be proven, in development, to be sufficient to span the batch and include samples from all types of areas including the areas where development has established the "worst" and the "best" uniformity results for all critical variable factors have been consistently found in addition to areas where the blend consistently has been found to have similar uniformity with respect to all critical variable factors – not just to the active or actives in the formulation. To ensure that you can obtain valid estimates of the within-sample variability and to provide a check for possible analytical bias, this reviewer must recommend that each unbiased sample should have unbiased duplicate "unit dose" (or smaller) aliquots removed and evaluated. The upper limit on the evaluation amount in any material should be "unit dose" because that is the drug products' nominal unit of uniformity.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
V Amendment Line number 216 (new text) (Continued)	(Continued) *Provided the inspection plan and decision schema are corrected in the manner suggested in this reviewer's previous remarks or an equally or more CGMP-compliant inspection-science conforming manner*, this reviewer suggests, *as does the commenter*, that finding of a failure should trigger an in-depth root-cause investigation designed to identify the root cause(s) of and the appropriate corrective actions for the failure observed. However, *because the sample-evaluation plan should include adequate safeguards (in the reviewer's view, duplicate "unit dose" aliquot evaluations with duplicate measurements of each aliquot) to ensure that, when an "analytical error" occurs, it should be detected before a result is certified and reported by the "laboratory" performing the sample analyses (and compensated for by evaluating an appropriate number of additional "unit dose" aliquots)*, this reviewer sees no need to address "analytical error" in this guidance as opposed to true result variability because in a CGMP-compliant laboratory results should only be reported and acted upon when the laboratory has certified the accuracy of the results. Returning to the commenter's suggestions, this reviewer essentially agrees with the commenter and suggests that the revised guidance contain the following language: "Identify the root cause of the failure. If the root cause is a mixing problem, we recommend that you proceed no further with implementation of the methods described in this guidance until you develop a new mixing procedure." However, this reviewer cannot agree with commenter's suggestion if the root cause of the failure is identified as a sampling related error and recommends the following text: "If the cause of the failure is proven to be a sampling-related problem, then take whatever root-cause-corrective actions are needed to solve the sampling-related problem and, after you verify that the root-cause-corrective actions are both valid and effective, resample the final blend." (Continued on next page)	(Continued) However, when the tablet is scored and the dosing directions include the breaking the dosage unit into halves or thirds and taking half or one-third, you should seriously consider blend sampling at the "half unit dose" or "on-third unit dose" level. Further, *for high dose tablets where the 80% or more of the formed dosage unit is a single active and the dosage unit weighs 100 mg or more*, you may sample at whatever sub-unit-dose weight level that your development studies has found to provide accurate estimates of the uniformity of the drug product's active uniformity and is optimal for minimizing the analytical uncertainty introduced by the procedure used to sample, work up, and evaluate the sample aliquots tested. Fundamentally, *for non-discrete materials*, it is *scientifically sound* and "doable" for you to sample large unbiased location representative multiple-dose samples that are appropriately larger in amount than the amount required for all projected evaluations for all critical variables, handle those samples in a manner that does not introduce any significant post-sampling variability changes into the sample, sample duplicate unbiased unit-dose or smaller aliquots from each blend sample, and work up and analyze the unbiased aliquots sampled. It is not scientifically sound for you to use a biased sampling procedure that repetitively samples biased "1-3 dose" amounts from ever differing locations from a less than *batch-representative* set of general locations and attempts to attribute any replicate sampling as being from the same "location" or claiming that the results from replicates in the same repeatedly disturbed general location are from the same "location" or to claim that, if necessary, you can go back and sample from the same location since every sampling changes the nature of the material in that "location." [**Note:** *Even if each sampling minimally disturbs the material in the location sampled*, then it should be obvious that a sound sampling plan that disturbs each location once for 2 tests for each of, for example, four (4) critical factors is better than a sampling plan that would need to sample each "location" no less than 12 times!] (Continued on next page)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
V Amendment Line number 216 (new text) (Continued)	(Continued) Using the new *batch-representative* unbiased samples from the approximately same locations in the final blend, or, *if the original samples were from the blend's production vessel and the blend has been transferred from that containment vessel into IBCs*, a double set from the locations that your sampling plans for IBCs normally require, and evaluate each sample sampled using duplicate 'unit dose' aliquots." Finally, this reviewer agrees with the commenter's final suggestion, "We also recommend that if you cannot identify the cause of the failing criteria that you do not proceed any further with implementation of the methods described in this guidance."	(Continued) Therefore, sampling plans that require the direct sampling of "n"-tuplicate "unit-dose" samples from potentially non-uniform and unstable mixtures are inherently less scientifically sound, *as most versed in the fundamentals of inspection science inherently know*, than single unbiased multiplicate-dose sampling from each location provided: a. Post-sample handling does not disturb the uniformity of the sample sampled and b. Sufficient unbiased "unit dose" (or smaller) aliquots are available for all replicates that may be required for all of the variable factors that must, because of the test methods used, be independently assessed.
V. "233"	Please clarify that this should reference footnote 9. While this reviewer and the commenter agree that the Draft references the incorrect footnote, this reviewer recommends that said footnote be removed because the application of the statistical techniques suggested in it is based on one or more false premises. [**Review Note:** Apparently, based on the line number discrepancies observed, from this point onwards, the commenter reviewed a draft other than the one published in ".pdf" format to the FDA's Draft Guidance e-documents folder with the file descriptor "03D-0493-gdl0001.pdf" in October of 2003. Generally, this reviewer has knowing chosen to" ignore," in most cases, the typically one (1) number difference between the commenter's line references and those in the published Draft.]	Footnote 8 refers to FDA/ORA Compliance Guideline, not the PDA Technical Report No. 25. The false premise that the **USP**'s RSD criteria are criteria that apply to a *representative sample* taken from the batch, when the reality is the **USP**'s sample criteria only apply to any non-representative "grab" sample taken from some small portion of the batch. Because, as the **USP's *General Notices*** clearly states, the **USP**'s procedures are NOT "statistical sampling plans," ALL of the "OC" curves and other comparison examples that follow are obviously NOT scientifically sound and, *at best*, misleading. [**Note:** If not an outright knowing effort to misrepresent factual reality to support patently invalid criteria that, *instead of being based on sound inspection science and, where possible, supported by the appropriate recognized consensus standards [ANSI an/or ISO*], are simply what the commenter wants to be able to get away with.]
VI "236-314"	We suggest reformatting these sections for clarity. Combine this section with section V to create a "validation" section. For the sound reasons cited in this reviewer's comments to the submissions of prior submitters who either suggested this course of action or, in their submission, attempted to do as this commenter suggests, this reviewer knows this should not be done – this section should remain a separate section.	The philosophy of the PQRI recommendation was to assess blend and in-process dosage units jointly, as evidenced by them being contained in the same flow diagram for the validation approach. Whatever the PQRI's philosophy, sound science, the precepts of the "costs of quality," and the CGMP regulations combine to make the practice proposed (use the weight corrected results from the testing of a few formed dosage units in lieu of performing any valid assessment of the uniformity of any prior non-discrete material produced during the manufacture of any batch) *not* ***legal*** *nor*, *as proposed*, ***scientifically sound*** *nor* ***CGMP compliant***. ***Moreover, assessing active uniformity is not a valid surrogate for assessing the batch uniformity of the drug product!***

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI. "237" Revised Attachment 1 And Table of Contents.	We suggest revising the title of section VI to: ANALYSIS AND CLASSIFICATION OF IN-PROCESS DOSAGE UNITS FOR BLEND UNIFORMITY ASSESSMENT. (Note this title is also used in the Revised Attachment and the Table of Contents) This reviewer disagrees with the commenter's suggestion and recommends that the title in the Draft should either remain as in the Draft, "**VI. VERIFICATION OF MANUFACTURING CRITERIA**" or be changed to the more informative: "**VI. VERIFICATION OF THE VALIDITY OF THE MANUFACTURING CRITERIA ESTABLISHED**" Otherwise, this reviewer recommends that this draft be replaced by the revised draft that was posted to the FDA Public Docket 2003D-0493 on 30 January 2004.	The proposed title more accurately reflects what is contained in this section. This section refers to the assessment of blend and dosage units against criteria and classification as "readily pass" marginally pass" or "inappropriate". Since the entire scheme proposed in the Draft is neither *scientifically sound* nor *appropriate*, how it should be viewed is of little consequence until the flawed plans proposed can be or are corrected. In addition, the scheme proposed does not comply with the CGMP regulations. Though this reviewer attempted to correct the deficiencies in the schemes proposed in the formal comments he submitted to FDA Public Docket 2003D-0493 in November 2003, his further review brought him the realization that the whole guidance is ***fundamentally flawed***. The ***fundamental flaw*** is that the published Draft ***improperly*** **attempts to equate the uniformity of the active** or actives in various materials **to the uniformity of the drug product with respect to all critical variable factors** (*assuring the uniformity and integrity of all critical variable factors* is what is clearly the *minimum* required by **21 CFR 211.110**). After recognizing the guidance was fundamentally flawed and, therefore, inherently not CGMP compliant, this reviewer used this Draft to generate a revised Draft, titled " "**Guidance for Industry Powder Blends And Dosage Units — In-Process Blend And Dosage Unit Inspection (Sampling And Evaluation) For Content Uniformity**" that this reviewer submitted, and which was posted to the FDA Public Docket 2003D-0493 on 30 January 2004.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI "240"	We suggest changing "normality" to "distribution of the data." This reviewer does not agree with the commenter's suggestion because the very "RSD" values they are computing are based on the assumption that the data is normally distributed. If the commenter finds that even evaluating the normality of the data is problematic, then this reviewer suggest that the commenter should propose testing the minimum number of *batch-representative* units required for a *distribution-free* assessment of the statistical properties of their samples from which they can validly project the probable limits of the active content of the dosage units in the batch for more than 99+ % of the population at a confidence level of at least 95 % (≥ 500 samples) or, failing that, use the appropriate similar range-based "AQL" estimates of distributional properties of the batch (only 230 samples). Is it perhaps that the commenter wants to remove the assessment of normality because the commenter knows that many of products have *significantly* non-normal (typically, bimodal) active content distributions because of the use equipment that is known to produce such materials (for example, ribbon blenders even those that meet their manufacturer's dimensional conformity tolerances [and few that this reviewer has seen seem to] that cannot continually recycle the significant percentage of the blend in the non-working volume [discharge valve] portion of such blenders into the working volume of the blender)? Hopefully, the Agency will disregard the commenter's baseless request or require those *who do not wish to asses the normality of the active results* to test the ≥ 500 *representative samples* minimally required to ensure that the limits observed can be validly presumed (at the 95 % confidence level) to encompass not less than 99 % of the batch's population.	A normal distribution is acceptable, but not required. A unimodal shape or bell shape with short tails (high peak of data in the center) while not a "normal" distribution is a preferred shape when describing batch uniformity. . To validly use normal statistics a near normal uniform distribution of values is required – not merely acceptable. Moreover, provided a batch-representative number of samples are tested and the results found are valid, for those who lack the appropriate computer programs, normality can be assessed by simply assessing how close the mean, median, and the mode are to a) the target and b) each other; the next simplest procedure (provided a *batch-representative number* of samples has been assessed) is to plot the frequency of values against the values and visually see if the distribution appears to be normal. Similarly the closeness of the computed mean value to the target and the symmetry of the range about the target should be assessed. [**Note:** If, *for batch-representative sets of samples*, you repeatedly find that your mean for the blend is several % lower (or higher) than the computed mean for the dosage units when the dosage units are tableted at target weight or the weight-corrected results for the dosage units are compared to the blend results, then you have a sampling bias that you should eliminate and/or are inspection or material issues that need to be thoroughly investigated and resolved.]

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI "282"	We suggest changing this line to read: "If your test results meet this criteria for all batches, they are classified as … ." If the Agency decides to use this Draft as its basis for providing guidance that is clearly restricted to *assessing the uniformity of the active or actives* and not to misrepresenting this guidance as if it can be used to "assess the uniformity … drug products," then, *unless the criteria are adjusted to be scientifically sound and meet today's "good manufacturing" distribution tolerances for variability ("six sigma")*, this reviewer would reject the commenter's suggestions and suggest changing the Draft's text to read" "If your test results meet these criteria, ~~they are~~ *the batch can be* classified as *readily ~~pass~~ passing* and, *provided: **a)** you have adequate controls on all of the chemical and physical properties of the components in your formulation, **and b)** all of the data for the development and other initial validation batches supports the batch-to-batch reproducibility of the results obtained,* you ~~can~~ *may be able to* start routine batch testing using the Standard ~~Verification~~ *Classification* Method (S~~V~~CM) described in section VII. If your test results fail to meet these criteria *for active uniformity* or the results *continually* come close to failing to meet one or more of these criteria, we recommend that you compare the results with the *marginally ~~pass~~ passing* criteria described below.""	This draft guidance does not explicitly state that all validation batches must pass in order to use SCM. This reviewer finds that the commenter provided no real scientific or regulatory justification for the change the commenter has proposed. As with any science-based decision, you need to require a foundation that consists of a consistent body of evidence that your process is truly operating in control. When you have that body of evidence, then, *provided you have adequate controls on all of the inputs to your process*, you may be able to select a standard approach that starts with the testing of less than the full number of batch-representative dosage units than a "normal" inspection plan requires (a "normal" sampling/"reduced" testing plan). However, you should still take the full set of *batch-representative* samples even when you feel justified in initially testing a batch-spanning subset instead of the full set sampled.
VI. "243-245"	The guidance should clarify the rationale for the classification values [readily pass (RSD ≤ 4.0%), marginally pass (RSD ≤6.0%) or inappropriate (RSD >6.0%)]. Though this reviewer agrees with the commenter that the rationale for the criteria selected needs to be addressed, this reviewer suggests that following alternative: "• For all individual results (for each batch, n ≥ ~~60~~ ***200***), the overall RSD ≤ ~~4.0~~ ***2.5*** percent. • *For all individual results (for each batch, n ≥ 200), the overall mean percent of the target value should be not less than (NLT) the target value percent. In practical terms:* $[\bar{x}_n + (t_{(0.975,n-1)} \times RSD / \sqrt{\{n-1\}})] \% \geq Target_{Process} \%]$ (Continued on next page)	Assigning values to the target values would help clarify this section. **For the Sample Number**, to be confident (at the 95 % confidence level) that the "normally distributed" results obtained for the samples tested apply to the batch, one must test not less than 200 representative units. Testing a smaller number reduces the level of confidence that one can have that the results found for the samples tested match those of the untested portion of the batch. Levels of confidence below "95 %" are not consistent with either CGMP or today's expectations for batch quality. **For the RSD**, since the post-release expectation (based on the **USP**'s *any-article* requirements) is that all units must be between 85 % and 115 % and the level of capability (C_P) for a process that corresponds to a "readily passing" batch is 2.0, the upper limit on the overall RSD (continued)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI. "243-245" (Continued)	(Continued) • Each ~~location~~ ***sampling-point*** mean is within ~~90.0~~ **95.0** percent to ~~110.0~~ **105.** percent of target strength. • All ***of the*** individual results are within the range of ~~75.0 ≥~~ ***85.0*** percent to ~~125.0 ≤~~ ***115.*** percent of ***the*** target strength."	(Continued) for the results from the testing of not less than 200 batch-representative units should be 2.5 percent – NOT the Draft's 4.0 (which roughly translates into a "process capability" of "1.25," a value that does not meet the recognized minimum value for even a marginally capable process. In today's "six sigma" quality world, a normally distributed product having its mean at 100 % of the target and an RSD of 2.5 % still translates into an expectation that the released batch may contain units that are outside of the **USP**'s expectation range. ***For the Mean***, a critical CGMP-compliance issue is whether or not the overall mean is sufficiently close to the target level to ensure that the CGMP formulation requirement set forth in **21 CFR 211.101(a)** **Sampling Point – Not** "location," as stated previously, the samples are from different points in time – not from different locations. **For the Range**, for a batch to be characterized as "readily passing," all of the results found must be within the **USP**'s "any article" *expectation range* and not its lifetime "no units can be outside of" range. This is the case because the percentage of samples tested is typically less than 0.1% of the batch and the expectation for such small samples is that all test results are within ± 3 RSD of the batch target for almost all possible distributions of active contents. In such cases, all test results should be inside of 85 % to 115 % of the permitted target because finding any outside of that range clearly establishes the reality that, post release, some sets of 30 will fail the **USP**'s uniformity of dosage units by content uniformity criteria for the active content and, if such articles are tested, the batch will fail. Therefore, the "readily pass" range must be "85 % to 115 %" ***or narrower*** – hence this reviewer ***recommends*** the following guidance: Results must be within the range: "**≥ *85.0* percent to ≤ *115.* percent of *the* target strength**."

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI. "244"	Express "marginally pass" as RSD greater than 4.0% and less than or equal to 6.0%. Again this reviewer cannot support the criteria in the Draft and proposes the following alternative set: "The RSD value *from the in-process results* should be used to classify the ~~testing results~~ *in-process core or capsule fill batch material* as either *readily ~~pass~~ passing* (*"n" ≥ 200,* RSD ≤ ~~4.0%~~ *2.5%*), *marginally ~~pass~~ passing* (*~~>4.0%~~ "n" ≥ 400,* RSD ≤ ~~6.0%~~ *2.5%*) or *inappropriate* for demonstration of batch ~~homogeneity~~ uniformity (*"n" ≥ 400,* RSD > ~~6.0%~~ *2.5%*). The procedures are discussed in the following sections:"	This change provides clarity. *Using a distribution-resilient "process capability" approach*, the RSD values in the Draft were revised to be congruent with an expectation range of from ≥ 85 % to ≤ 115 % of the targeted level with a "C_P" of 1.34 for the *marginally passing* level and "C_P" of 2.0 for a *readily passing* level.
VI "250"	We recommend changing the wording of this section to: "Prior to the manufacture of the batch, carefully identify locations…" ***For overall uniformity***, this reviewer supports the commenter's suggestion here: "Prior to the manufacture of the batch, carefully identify ~~locations~~ sampling points throughout the compression or filling operation to sample in-process dosage units. Your selection should be done in a manner that ensures the points selected encompass the dosage-forming phase of the manufacture of the batch. The sampling locations should also include significant process events (such as**,** hopper changeover~~,~~ ~~—~~and hopper ~~—~~filling**,** ~~or~~ machine shutdown and restart, and the beginning and end of the compression or filling operation~~.~~[16]*)* that are outside of the dosage-forming machinery's normal operating envelope. There should be at least 20 locations ~~with 7 samples each for a minimum total of 140 samples~~ at which you sequentially sample a number of dosage units that is some integer multiple of the dosage-unit forming stations in the system being studied for a minimum total of not less than 600 units for *each variable factor* that needs to be evaluated ~~for~~ to comply with the representative sample sampling requirements of the drug CGMP regulations (**21 CFR 211.160(b)(2)**). In general, the samples at each sampling point should be placed in a suitable separate labeled container. These include periodic sampling locations and significant-event ~~locations~~ sampling points**.** [16] The beginning and end samples are taken from dosage units that would normally be included in the batch." (Continued on next page)	The current wording does not explicitly state that sampling locations should be determined "prior" to the validation exercise, as the PQRI proposal does. **Commenter's First Statement:** In the planning process for the dynamic sampling of a production phase, the sampling needs to be defined in terms of "*points*" rather than "locations." [**Note:** This is the case because the ***location*** of the sampling (the discharge chute from the dosage forming equipment) remains fixed and the sampling points are separated by time rather than location.} *While this reviewer has no problem with the total number of points*, valid unbiased "*process representative*" dynamic sampling requires the sampling of not less than one dosage unit from each dosage-forming unit station at each sampling point. Typically, because the samples collected are used for both variable factor testing and attribute factor examination, some integer multiple of that number of dosage units is sampled at each sampling point. Because the manufacturer needs to be highly confident (a confidence level of 95% or higher) that their findings are truly predictive of the results that would be found if the entire batch were tested, NLT 200 *batch-representative* units (made up of an equal number of randomly selected units from the process-representative sample units collected at each sampling point) need to be tested for the single variable factor, active content, being addressed in this guidance. The need for testing such a 200-unit sample is dictated by: (Continued on next page)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI "250" (Continued)	(Continued) (Consider adding a cross-reference to Section IV-B as the recommended approach.) This reviewer sees no compelling reason to make this change.	(Continued) a. The lack of rigorous controls on each of the physical properties that affect the uniformity achieved each time a defined processing step set is performed using components whose properties vary in a complex undefined manner. b. The need for a confidence level of 95 % or higher in the validity of the estimation of the acceptability or non-acceptability of the batch at the end of this process phase. c. The numbers required by the applicable recognized statistical consensus standards ("**ISO 3951**" or "**ANSI/ASQC Z 1.9**") for evaluating batches of discrete units for the normal inspection, "process variability unknown—SD" case, and d. A lack of sufficient production history to justify the use of a hierarchical sampling plan that initially tests a consensus-standard-recognized defined subset (50 *representative* units in this case) and then proceeds in different pre-established manners depending upon the outcome observed for the initial subset tested. **Parenthetical Comment:** The commenter offered no rationale here Since Section VI and the prior ones logically proceed from subsection to subsection, there is no need to add further logical clutter by adding a parenthetical reference to the next subsection in the current subsection.
VI - A "257-258"	Please consider adding at the end of the bullet: "Assay all 7 per location if required in Section V." Though this reviewer does not support this addition, this reviewer does recommend revising the cited **Lines 258-259** in the published to: " • ~~Assay at least 3 of the 7~~ *For a 20-point sampling, select, at random, 10 units from each sample point, weigh each, work up each unit in a manner that preserves the link between each unit's identity and its weight, appropriately test the each worked up sample, determine the results for each sample,* ~~and~~ weight correct each result *and appropriately tabulate the results found.* (**Note:** *Should you wish to evaluate a lesser number*, ~~T~~*t*he number of samples to evaluate from each sampling point should be specified and justified for a given product and process.)"	There is no connection back to the performance of the blend (Sec. V). If one has to assay 7 per location to satisfy blend homogeneity, the same samples may be used to demonstrate in-process performance. Since this section (Section VI) discusses the "verification" of the adequacy of the blend specifications as established for full-scale conformance batches for the single critical variable factor uniformity, "active uniformity," the evaluation should require the assessment of not less than 200 batch-representative dosage units appropriately selected for the samples at each sampling point. As with all scientifically sound inspection plans for materials made in batches, a body of consistently conforming outcomes is needed before any reduction in the inspection level (number) can be justified (typically not less than ten (10) consecutive successful "routine production" batches after not less than "3" consecutive successful conformance batches).

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI - A Between "258 and 259"	We recommend adding: "Analyze the dosage units according the flowchart in Attachment 1." This reviewer does not agree with the commenter's suggestion and recommends that this change not be made.	There is no connection back to the flowchart in Attachment 1. The PQRI document provides acceptance criteria for the stage 1 data (3 per location) and also provides stage 2 sample sizes and acceptance criteria. See this reviewer's remarks in Row "VI - A '257-258'"
VI - A Amendment line number 260 (new text)	We suggest revising this section to: "Conduct an analysis of the dosage unit stratified sampling data to assess the active ingredient distribution throughout the batch (e.g., visual assessment of a histogram or a probability plot). Indications of trends, bimodal distributions, or other forms of a distribution other than bell-shaped should be evaluated." Though this reviewer agrees with the commenter that this bullet point needs to be revised, this reviewer suggests it be changed to: • Conduct an analysis of the dosage–unit ~~stratified~~ dynamically sampl~~ing~~ed ~~data~~ weight-corrected results to demonstrate that the results obtained for the batch-representative samples tested indicate that the dosage units in the batch probably ~~has~~ have a *near* normal active-content distribution ~~of active ingredient~~. At the simplest level, one can determine the mean, median and mode values for the data set – when they are, within the observed result uncertainty, the same, the level of active in the batch of tablets can be presumed to be normally distributed. If this simple test is inconclusive, then you should construct a frequency bar graph depicting the frequency of values in a given narrow value range interval on its "Y=axis" against the mean active level in the interval increments specified on the "X-axis," and examine this chart and the tabulation of the results versus time point. Indications of trends, bimodal distributions, or other forms of a distribution other than normal should be investigated. If any of these ~~occurrences~~ conditions significantly affect your ability to ensure batch ~~homogeneity~~ uniformity of the active(s), ~~they should be corrected~~ the root cause or causes for the non-uniformity of the results should be identified, appropriate corrective actions implemented, and the studies repeated until the results indicate that the batch is sufficiently uniform with respect to the level of active in the dosage units."	A normal distribution is acceptable, but not required A unimodal shape or bell-shape with short tails (high peak of data in the center) is not a "normal" distribution, but it is a preferred shape when describing batch uniformity. . The commenter's rationale again misstates the reality that a normal distribution is the preferred distribution but that many near-normal unimodal or bell-shaped distributions are acceptable distributions where it is valid to use "normal" statistical procedures to describe the approximate dispersion of the critical variable factors' results about the calculated average value and predict the batch's dispersion of these critical variable factors, including the active(s) about the batch's targeted mean value. The critical caveats are: a. The samples tested must be *representative* of the batch and b. The number tested must be sufficient to provide a high level of confidence (typically, at the 95 % confidence level or higher) that the outcomes observed for the samples tested do, in fact, reflect the untested units in the batch. For the "full scale" conformance batches for which this procedure applies, the *minimum* number of dosage units that should be tested (for each primary critical variable factor) is NLT 200 *batch-representative* units.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI - A "265"	Change "normality" to "distribution (e.g., unimodal, bell-shaped, normal) Provided the text is changed to order the types of distributions from the most acceptable to the worst as shown and include distributions for which the procedures shown are not appropriate, this reviewer supports replacing "normality" with "distribution (e.g., …)." This reviewer suggests: Change 'normality' to 'distribution (e.g., normal or Gaussian, skewed Gaussian, bell-shaped, Poisson, unimodal, bimodal, rectangular, wedge-shaped, hyperbolic, disjoint)' in line 266." In addition, the bullet point containing the first change should be revised to: "• Prepare a summary of this analysis. ~~Potential~~ ~~i~~Investigation results along with a description of batch normality should be included in ~~the~~ this summary. ~~Submit~~ For your drug product submissions to the Agency for review, you should include the results' data and this summary with the ~~application~~ submission as described in section VIII of this guidance."	A normal distribution is acceptable, but not required. The proposed change should include examples of distributions that are unacceptable as well as those that are or may be acceptable. In addition the text associated with this bullet point also needs to be revised as shown.
VI - A 268	Please consider removing the phrase In addition to this analysis of batch normality" and replace with Additionally, we recommend… ." This reviewer supports the commenter's suggestion, but understands that the rest of the sentence also needs to be revised to: ""~~In addition to this analysis of batch~~ Additionally, provided the results obtained are acceptable, we recommend that you classify the test results as *readily* ~~*pass*~~ ***passing*** or *marginally* ~~*pass*~~ ***passing*** according to the following procedure:"	Reference to normality does not add to the meaning of this section. The text changes proposed should include restricting the classification to those active content result sets that indicate the batch has an acceptable active uniformity. When the results are unacceptable, you should initiate the appropriate in-depth "root cause" investigation and, when the cause(s) is(are) identified, implement the appropriate "root cause" CAPA plan before proceeding with the classification scheme proposed.
VI - B "273"	We suggest revising this section to read: "For each separate batch, compare the weight-corrected test results to the following criteria." This reviewer cannot agree with the commenter's suggestion because it is at odds with the clear in-process CGMP requirements that require the active's dosage-unit uniformity to be evaluated on "**the characteristics of in-process material**"; the weight-corrected active is not a characteristic of the in-process dosage units – it is a biased characteristic, and suggests the following CGMP-compliant alternative: "For each ~~separate~~ *individual* batch, compare the dosage-unit test results to the following criteria:" (Continued)	The recommended changes would help the draft guidance reflect the intent of the PQRI proposal **21 CFR 211.110(a)**, "…Such control **procedures** shall be established to **monitor the output and to validate** the performance **of** those manufacturing **processes** that **may be** responsible for **causing variability in the characteristics of in-process material** and the drug product." All that the *weight-corrected formed dosage-units active-content results* should be used for is to compare the *weight-based blend results* to the *weight-corrected formed-dosage units results* in instances where such comparisons are valid – this is clearly not the case here. (Continued)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI – B "273" (Continued)	(Continued) In addition, the rest of this section (Lines 276-285) should be revised to: "• For all individual results **for each active individually** (for each batch**,** n ≥ ~~60~~ **200**)**,** the overall RSD ≤ ~~4.0~~ **2.5** percent. • For all individual results **for each active individually** (for each batch**,** n ≥ 200)**,** the overall mean percent of the target value should be not less than the target value percent. In practical terms, this requirement translates into: $[\bar{x}_n + (t_{(0.975,n-1)} \times RSD / \sqrt{\{n-1\}})]\ \% \geq Target_{Process}\ \%$. • Each ~~location~~ sampling-point mean is within the relative range of ~~90.0~~ **≥ 93.0** percent to ~~110.0~~ **≤ 107.** percent of target strength. • All of the individual results are within the relative range of ~~75.0 ≥~~ **85.0** percent to ~~125.0~~ **≤ 115.** percent of the target strength or, ***failing that***, not more than 1 in 200 tested are outside of 85.0 percent to 115. percent, and none are outside of the relative range of 80.0 % to 120 % of the target strength. • The results meet the batch acceptance criteria for your established AQL level when the results are evaluated against the 'process variability unknown—standard deviation' criteria for 'normal inspection' in ISO 3951 (or ANSI Z1.9, its American equivalent)." If your test results meet all of these criteria, ~~they are~~ the active results can be classified as *readily ~~pass~~* passing and, provided you have adequate controls on all of the physical properties of the components in your formulation, all of the data for the development and the other initial conformance batches supports the batch-to-batch reproducibility of the results obtained, you ~~can~~ may be able to start routine batch testing using the Standard ~~Verification~~ Classification Method (SC~~V~~M) described in section VII. If your test results fail to meet any of these criteria, we recommend that you test an additional set of samples and compare the results found for the combined sets with the *marginally ~~pass~~* passing criteria described below." [**Note:** The importance of meeting the "85 % to 115 % of target" range cannot be over emphasized.]	(Continued) **For RSD and Individual Results:** For a batch to be characterized as "readily passing," all of the results found should be within the **USP**'s "any article" *expectation range* and not just its lifetime "none" range. This is the case because the batch percentage tested is typically less than 0.1%. Thus, almost all results must be inside of 85 % to 115 % of the permitted target because finding any outside of that range clearly establishes the reality that, post release, some sets of 30 may fail the **USP**'s "post release" content uniformity criteria by having more than 1(for "tablets") or 2 (for "capsules") outside the expected range, and, if such 30's are tested, the batch will fail. **For Set Mean:** A critical CGMP-compliance issue (that the Draft seems to ignore) is whether or not the overall mean is sufficiently close to the target level to ensure that batch meets the CGMP formulation requirement set forth in **21 CFR 211.101(a)**. **For Sampling-Point Means:** As stated previously, the samples are from different time points not from different locations. Moreover, since the expectation for all individuals in small samples should be that they are mostly in the relative range from 92.5 % to 107.5 % (based on the RSD for this category), the means expectation range should be inside of the expected values range. Furthermore, the mathematical precision should be the same for both limits **For Individual Active's Results:** For a batch to be characterized as "readily passing," almost all of the results found must be within the **USP**'s "any article" *expectation range* and not its lifetime "no units can be outside of" range. This is the case because the tested % of the batch is typically less than 0.1%. In such cases, all results should be inside of 85 % to 115 % of the permitted target because finding any outside of that range clearly establishes the reality that, post release, some sets of 30 in the batch may fail the **USP**'s content uniformity criteria by having more than 1 (for "tablets" or 2 ("for capsules") outside the expectation range, and, when such 30's are tested, the batch will fail.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI – B "273" (Continued)	(Continued) This is the case because, after release, the finding that more than **1 in *any* 30 "tablets"** or **2 in *any* 30 "capsules"** tested has an active level that is outside of "85 % to 125 % of the Label Claim or, if higher, the **USP Assay** mid-range percentage fails the entire "in commerce" batch. *In any batch*, the **risk** of finding 2 tablets or 3 capsules in 30 outside of "85 to 115" is at least an order of magnitude greater than finding 1 in 30 outside of "75 to 125."	(Continued) **Batch Acceptance Criteria:** This reviewer notes that the Draft failed to mention, much less address, the issue of setting acceptance criteria for the batch based on the results found from the testing of a small percentage (typically, less than 0.1 % and in an increasing number of cases less than 0.01 %) of the batch even though such acceptance criteria are clearly needed and, for the drug product units tested for acceptance for release, are explicitly required (**21 CFR 211.165(d)**). After all, it is the untested part of the batch that the patients will be prescribed. To address the Draft's omission, this reviewer has provided corrective language. **Handling Non-Acceptable Batches:** When initially attempting to finalize the *scientifically sound specifications* and *acceptance criteria* that you have established for the batch based on the testing of a small batch-representative percentage (0.1% or less) of an initial conformance batch where the true variability and distribution of the dosage units in the batch are <u>not</u> known with certainty, the only valid way to address a conformance batch that does <u>not</u> meet its acceptance criteria but contains no failing units (those outside of a relative range of 75.0 percent to 125 % of the target strength) is to test additional samples to obtain: a. A better estimate of the real active content limits of the batch and the distribution of units in the batch, and b. Ascertain whether, or not, the values observed and their batch implications justify accepting a batch using an augmented inspection plan to assess the acceptability of the batch with respect to its uniformity of the active or active(s) present. *After the testing of at least 3 consecutive acceptable conformance batches*, then you should be able to review the entire set and devise an acceptable staged inspection plan that should still take full samples but may <u>validly</u> test as few as 50 batch-representative dosage units for conformance to a valid "reduced" inspection criteria for your Stage 1 plan (this reviewer recommends a Stage 1 plan of "80" units when the batch exceeds 1,000,000 units), a 200-unit Stage 2 plan using these criteria, and a 400-unit Stage 3 plan based on the "marginally passing" criteria that follow.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI - C "289-291"	We suggest revising this section to read: "If your dosage unit test results fail to meet the criteria for the readily pass classification, compare the weight corrected results to the following criteria." This reviewer cannot support the commenter's suggestion because it conflicts with clear in-process CGMP material assessment requirements that require the ***characteristics*** of the material to be assessed, not some "*weight-variability corrected*" *characteristic* as the commenter is again proposing. Provided the Draft is revised to limit the scope to the content uniformity of the active, this reviewer suggests the following CGMP-compliant alternative: "If your dosage unit test results fail to meet the criteria for the r*eadily passing* classification, you should first investigate the findings to see if there are any processing factors associated with a given sampling point that may have cause the data at that point to one or more results that either caused the batch not to meet a given "readily passing" criterion. This is especially important in cases where the problem point or points are associated with "significant events," (like the start of dosage unit formation or the end of dosage-unit formation or an equipment-related interruption and restart), where the procedure may easily be changed (for example, changing the end of formation point from "after the last of the final blend has been loaded into the hopper, continue running until the level of blend in the hopper reaches the '25 %' full mark" to "after …into the hopper, continue running until the level … reaches the '50 %' full mark) to reduce the risk of an excursion. If any valid result is outside of the range from 75 % to 125 % of target, all that you should do is investigate and revert to the formulation development stage because the current process obviously does not reliably produce in-process units that meet the CGMP minimums. ***In some cases***, you may be able to justify evaluating ~~assay the remaining dosage units (all 7 units per location)~~ another set of dosage units and ~~compare~~ comparing the test results for the combined sets to the following criteria:"	This change is necessary to comply with the Amended line 283, which describes how many to test. In addition, it helps clarify that the data are weight corrected for those not familiar with the PQRI proposal. This reviewer already addressed this issue in his basis statements in Row IV - B "273" When one finds results outside of those expected, the first thing that they should do is review the results and look to see if the unexpected results have a possible cause that can be addressed by a change in procedure. For example, if the most of the results for "Point 22" are much different that the results found for "Point 21" or "Point 23" and "Point 22" corresponds to a "significant event" such as "restart after tooling change" look to see what can be done to change the restart procedure and/or the point at which formed dosage units are again collected as part of the batch that could reduce the risk of including such "different" units into the batch of dosage units suitable for further processing. However, unlike the **USP**'s "grab sample" approach (directly applicable **only** to "in commerce" drug product) where one can justify the relaxation of the acceptance criteria for sample average properties like the mean and the RSD when the testing is expanded from one level of units to a larger number of units, sampling that complies with the CGMP should yield results that give "mean" and "RSD" values that are respectively: a. Closer to the target level and b. Smaller or certainly not larger than the value found for the smaller number of ***batch-representative*** samples tested. Thus, to even propose to widen the RSD for acceptability, those that wrote the Draft are "admitting" that the sampling and testing plans they propose do not reflect the CGMP minimum requirement that both must be *representative of the batch*. Moreover, during criteria verification it is important to increase testing whenever the initial testing results do not meet the *scientifically sound sample specifications* and *batch acceptance criteria*.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI – C "293"	We suggest revising this to read: "…results (for each batch n > 60) the … ." This reviewer cannot support the commenter's suggestion. This reviewer offers the following inspection-science-based, CGMP-compliant alternative: "If your dosage unit test results fail to meet the criteria for the r*eadily passing* classification, you should first investigate the findings to see if there are any processing factors associated with a given sampling point that may have cause the data at that point to one or more results that either caused the batch not to meet a given "readily passing" criterion. This is especially important in cases where the problem point or points are associated with 'significant events,' (like the start of dosage unit formation or the end of dosage-unit formation or an equipment-related interruption and restart), where the procedure may easily be changed (for example, changing the end of formation point from 'after the last of the final blend has been loaded into the hopper, continue running until the level of blend in the hopper reaches the 25%- full mark' to 'after …into the hopper, continue running until the level … reaches the 50%-full mark') to reduce the risk of an excursion. If any valid result is outside of the range from 75 % to 125 % of target, all that you should do is investigate and revert to formulation and process development since the current process does not reliably produce in-process units that meet the CGMP ***minimums***. ***In some cases***, you may be able to justify evaluating ~~assay the remaining dosage units (all 7 units per location)~~ another 200-unit batch-representative set of dosage units and ~~compare~~ comparing the test results to the following criteria:" • For all individual results (for each batch*,* n ≥ ~~140~~ *400*)*, the overall* RSD ≤ ~~6.0~~ *2.5* percent." • For all individual results (for each batch**,** n ≥ 400)**,** the overall mean percent of the target value should be not less than the target value percent. In practical terms: **$[\bar{x}_n + (t_{(0.975,n-1)} \times RSD / \sqrt{n-1})] \% \geq Target_{Process} \%$.** (Continued on next page)	The commenter provided no supporting rationale. This is the case because the commenter's suggestion does not test an adequate number of batch-representative units that is appropriate for conformance batches that typically contain more than 250,000 dosage units, especially when the initial testing does not meet the Draft's *readily passing* criteria. When one finds results outside of those expected, the first thing that they should do is review the results and look to see if the unexpected results have a possible cause that can be addressed by a change in procedure. For example, if the most of the results for "Point 22" are much different that the results found for "Point 21" or "Point 23" and "Point 22" corresponds to a "significant event" such as "restart after tooling change" look to see what can be done to change the restart procedure and/or the point at which formed dosage units are again collected as part of the batch that could reduce the risk of including such "different" units into the batch of dosage units suitable for further processing. However, unlike the **USP**'s post-release, any "grab sample" (*article*) approach where one can justify the relaxation of the acceptance criteria for sample average properties like the mean and the RSD when the testing is expanded from one level of units to a larger number of units, sampling that complies with the CGMP should yield results that give "mean" and "RSD" values that are respectively: a) closer to the target level and b) smaller, or certainly not larger, than the value found for the smaller number of batch-representative samples tested initially. Thus, to even propose to widen the RSD for acceptability, those that wrote the Draft are "admitting" that the sampling and testing plans they propose do not reflect the CGMP minimum requirement for that both must be representative of the batch. **For RSD:** For a batch to be characterized as "marginally passing," the representative samples' active content results' $RSD_{n \geq 400} \leq 2.5$ %. (Continued on next page)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI – C "293" (Continued)	(Continued) • Each ~~location~~ sampling-point mean (for 20 units chosen at random from the number collected at each sampling point) is within ~~90.0~~**94.0** percent to **106.**~~110.0~~ percent of target strength. • All individual results are within the range of 75.0 percent to 125.0 percent of target strength, not more than 1 unit in the 400 tested is outside of the range from 80 % to 120 % pf the target strength, not more than six (6) units in 400 units tested is outside of the range from 85 % to 115 % of the target strength, and no test point of 20 contains more than one (1) unit that is outside of the 85 % to 115 % range. • The lesser of |115. – $\bar{x}$| or |$\bar{x}$ – 85.0| divided by (3.27 x $RSD_{n=400}$) is not less than 1.5. "If your test results meet these criteria, ~~results~~ the ***batch*** can be classified as *marginally* ~~*pass*~~ ***passing***. If your samples do not meet these criteria, we recommend that you investigate the failure, find justified and assignable cause(s), correct the deficiencies, and repeat the powder mix homogeneity assessment, in-process dosage unit sampling ~~correlation~~ comparison, and initial criteria establishment procedures. The disposition of batches that have failed the m*arginally pass* criteria is outside the scope of this guidance. However, because these are not "*passing*," the CGMP regulations in **21 CFR 211.110** clearly require such materials to be rejected (**21 CFR 211.110(c)** 'In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.') and quarantined (**21 CFR 211.110(d)**, 'Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.') <u>until</u> their deficiency or deficiencies can be corrected."	(Continued) **For Sampling-Point Means:** As stated previously, the samples are from different time points not from different locations. Moreover, since the expectation for all individuals in small samples should be that they are within the relative range from 92.5 % to 107.5 % (based on the RSD for this category), the means expectation range should be inside of the expected values range and slightly narrow as the number of sample aliquots tested increases. **For Individual Active's Results:** For a batch to be characterized as "marginally passing," most of the results found should be within the **USP**'s "any article" *expectation range* and not its lifetime "no units can be outside of" range. This is the case because the tested % of the batch is typically less than 0.1%. In such cases, most all results must be inside of 85 % to 115 % of the permitted target because finding more than 15 in 1000 outside of that range clearly establishes the reality that, post release, some sets of 30 in the batch may fail the **USP**'s content uniformity criteria. **Batch Acceptance Criteria:** This reviewer notes that the Draft failed to mention, much less address, the issue of setting acceptance criteria for the ***batch*** based on the results found from the testing of a small percentage (currently, less than 0.2 % and in an increasing number of cases less than 0.02 %) of the batch even though such acceptance criteria are clearly needed and, for the drug product units tested for acceptance for release, are explicitly required (**21 CFR 211.165(d)**). **After all, it is the untested part of the batch that the patients will be prescribed.** To address the Draft's omission, this reviewer has provided corrective language.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI.D. "308-315"	Please consider moving Sub-section VI.D to Section VII. This reviewer does not support the commenter's suggestion to move this Subsection because its placement is logically correct. However, because the section covers more than just deciding "sampling locations," this reviewer recommends that this Subsection be re-titled and revised as follows: " **D. Summary of Findings and Setting the Inspection Plan For Routine Manufacturing** 1. Findings Summary We recommend that you prepare a *scientifically sound and justified* summary of ~~the~~ your in-process data analysis from the powder mix assessment and ~~stratified~~ dynamically sampled, batch-representative formed- dosage-unit sample testing studies that you have performed. 2. Routine Manufacturing Inspection a. The Final Blend From the blend analysis for all conformance batches, establish the minimum set of sampling locations (typically, NLT 5 for sampling from the blend's container and "n+2" when sampling from an ordered set of "n" drums) that, on average, give the same uniformity picture as the full sets sampled. Set your inspection plan to take duplicate samples from the furthest apart locations and the mid-point location and singlicate samples from the remaining samples to provide some estimates of within-location variability (about 8 test aliquots for the container samples and about "n+5" for the IBCs. Make the acceptance criteria and post-acceptance decision criteria as follows: 1) If blend samples tested meet all blend acceptance criteria, set the routine dosage-unit testing to start at **Stage 1**. 2) If the blend samples tested meet the range criterion but not the other criteria, set the routine dosage-unit testing to start at **Stage 2**. 3) If the blend samples do not meet the range criteria but are all in the range of from 87.0 % to 113. %, set the routine dosage-unit testing to start at **Stage 3**. (Continued)	It is more appropriate to place this section under "ROUTINE MANUFACTURING" rather than under "VERIFICATION OF MANUFACTURING CRITERIA." Subsection VI.D addresses much more than assigning sample locations for the blends and sampling points for the formed dosage units and is properly placed. All that needs to be corrected is its title and, in some areas, its language. Those who drafted this portion of the guidance seem to be attempting to turn a CGMP requirement (**21 CFR 211.160(b)(2)**) that the in-process sampling be *representative* of the batch into an explicit guidance "suggestion" that choosing a number of points "to represent" the batch somehow satisfies this CGMP requirement when it does not *per se* do so. The reality is that this juxtaposition of terms, "to represent the entire routine manufacturing" for the clear regulatory requirement of **21 CFR 211.160(b)(2)**, "Such samples shall be representative and properly identified," is neither *scientifically sound* nor CGMP-conforming. This is the case because the samples from any set of points, including those from sets that are not *batch representative*, can be validly held "to represent" the properties of the batch. However, only those samples from sampling point sets that meet the requirements for a dynamically sampled *batch-representative* set can meet the CGMP requirement set forth in **21 CFR 211.160(b)(2)**. Thus, the guidance should specifically require the selection to include the start point (just after the manufacturer begins to collect the formed units as a part of the batch) and the end point (the last units included in the batch) because, for a *dynamically sampled sample* must span the batch to be "batch representative", as required by the CGMP regulations. Therefore, this reviewer has altered the Draft text to reflect the preceding factual scientific and regulatory realities.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI.D. "308-315" (Continued)	(Continued) 4) If any of the blend samples' results are outside of the range in Step "3)," refer the Batch to the QCU and proceed as they direct. b. The In-Process Dosage Units 1) From the data analysis, you should establish the ~~stratified~~ dynamically formed dosage-units' sample locations for routine manufacturing, taking into account significant process events and their effect on in-process dosage unit and finished dosage unit quality attributes. 2) You should identify *and designate* ~~at least 10~~ not less than 10 "routine production" sampling ~~locations~~ time points (the start point, the end point, and not less than 8 approximately evenly spaced intermediate points) during capsule filling or tablet compression ~~to represent~~ that your studies have established to be approximately as representative of the entire routine manufacturing of the formed units that comprise the batch as the entire set while making provision for the inclusion of any 'significant events' that may occur during this production step. 3) In addition, the number sampled at each point should be appropriately adjusted to be that integer multiple of all of the dosage forming stations in the forming system that is required to satisfy all of the firm's pre-established sampling and sample evaluation (examination and testing) for the said formed units. 4) You should use the outcomes from the blend testing to guide you as to the number of *representative samples* that you need to *randomly* select for analysis from the full set sampled at each location (for example, *if you have 10 sampling points*, 5 at random for **Stage** 1 [50], 20 at random for **Stage 2** [200] and 40 at random for **Stage 3** [400]. [**Note:** You should continue to use the outcomes observed to refine your decision making and physical material controls within the AR and CBE-0 flexibility permitted by the Agency. When you have accumulated a sufficient history of continuously passing batches at both the blend and the formed-dosage material and the data clearly support that your production batches are all consistently close to their targets, you may be able to establish and justify switching to a set of inspection plans would permit you to use the applicable ISO (continued)	

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VI.D. "308-315" (Continued)	(**Note** continued) (ANSI) "process variability known" (PVK) plans to further reduce the drug-product starting point test sample numbers while still preserving the ability to use the existing plans should the results indicate that such a step is required. These "PVK " plans would, contingent upon the AQL level appropriate to your product (0.10 to 1.5 % nonconforming), allow you to have a Stage A (reduced inspection) plan that need only test 12 to 22 units, and a Stage B (normal inspection) plan that need only test 42 to 71 units coupled with the permissible option to switch to the "process variability unknown" ("PVU") case plans at Stage 2 and proceeding from there as "PVU" set guides you. Thus, those who develop truly uniform robust blends should be able to justify routinely testing for as few as 8 (blend vessel) to about 15 (blend-IBCs) batch-representative blend samples and 12 (or, if your firm is "6 sigma" quality oriented, 17) batch-representative samples when your history truly supports a 0.1 % AQL.]"	
VII. "320-322"	We recommend adding a statement that routine testing of powder mixes can be replaced by testing stratified samples. This reviewer must reject the commenter's suggestion for the following reasons: 1. The in-process CGMP regulations for drug products (**21 CFR 211.110**) clearly require the uniformity assessment of each batch at each discrete phase (including the final blend phase of production) for all critical variable factors (including active level, release-control ingredient level, lubricant level, etc.) if the variability in such may adversely affect the characteristics of the in-process material and the drug product. 2. In the *Barr* opinion (¶ 64), one of Judge Wolin's findings was blend testing is required for "ordinary production batches." 3. In the 1988 US Supreme Court decision in Berkovitz v. USA, the Court unanimously held that it is not legal for an FDA administrator to publish any document that is at odds with any clear FDA regulation. 4. In 1992, GDEA criminalized the "subversion of the regulatory process," gave the Secretary of HHS the authority to initiate debarment proceedings against any person whose actions constitute an attempt to subvert the regulatory process, and revised the Federal Food, Drug, and Cosmetic Act ("FDC Act"). (Continued on next page)	The change would make explicit that one of the key advantages of this guidance is to allow the manufacturer to do in-process testing of dosage units instead of testing the powder mix for routine production. **21 CFR 211.110(a)** **21 CFR 211.110(c)** **21 CFR 211.110(b)** **USA v. Barr Laboratories, Inc., et al.**, Civil Action No. 92-1744, (**812 Federal Supplement 458 (DNJ) 1993**, "Barr Opinion". **Berkovitz v. US, Supreme Court 1988, 486 US 531, 100 L Ed 2d 531, 108 S Ct 1954**. **Generic Drug Enforcement Act of 1992**" – Pubic Law. 102-282, Sec. 1(a), May 13, 1992, **106 Stat. 149**, provided that: "This Act [enacting sections 335a to 335c of this title {**FDC Act**}, amending sections 321, 336, 337, and 355 of the title {**FDC Act**}, and enacting provisions set out as notes under section 335a of this title {**FDC Act**}] may be cited as the '**Generic Drug Enforcement Act of 1992**'." This "*title*" is commonly abbreviated as "**GDEA**" (Continued on next page)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VII. "320-322" (Continued)	(Continued) 5. The fundamental precepts of the "cost of quality" support the reality that finding non-conforming materials as early in a multi-step production process as possible costs the manufacturer less than finding the same problem after the product is shipped to the customer – yet firms continue to knowingly develop and use material, process, and product controls that seemingly do not comply with the applicable CGMP ***minimums***. 6. Finding that a final blend is less uniform than it should be can usually be easily corrected by re-blending the drug product coupled with adding a small amount of additional lubricant and, if needed, the release-control agent during the reblending, and adjusting the blend target appropriately lower with a similar increase in the tablet weight is usually sufficient to bring a slightly out-of-specification blend into the acceptable uniformity band for the blend. Attempting to reprocess "failing" tablets or, worse still, capsules back into a blend and then making the appropriate ingredient adjustments in a reblending step is a much more expensive proposition with a much less certain outcome. Simple economics would dictate that a firm would want to be sure their final blend was "in spec" before committing proceeding. Yet, this commenter and the PQRI have, and have had, the hubris to knowingly recommend guidance that is at odds with the law, science, and sound economics as well as produces drugs that are not only adulterated but also have, in some cases, injured some who took these adulterated drugs. This reviewer can only hope that the Agency will see through the commenter's apparently self-serving actions and, as the Agency has done previously, reaffirm the lawful position that it is not legal for a manufacturer not to assess the uniformity of each blend. (Continued on next page)	(Continued) Perhaps the 2002 consent decree that included a $ 500,000,000.00 fine and other costs associated with Schering-Plough's in-process failure to properly assess and control the uniformity of the active ingredient(s) in the formed dosage units, inhalers in this instance, prior to their releasing each batch of some of their drug products is an indication of the order of magnitude of the potential costs to a regulated drug product manufacturer if it knowingly does not assure the uniformity of the firm's drug products. FDC Act at **21 U.S.C. 351(a)(2)(B)** explicitly states: **"A drug … shall be deemed to be adulterated — if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess"** **21 U.S.C., Chapter 9,** SUBCHAPTER III—PROHIBITED ACTS AND PENALTIES, 21 U.S.C. **Sections 331 through 337.** (Continued on next page)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VII. "320-322" (Continued)	(Continued) In addition, the commenter's suggestion is at odds with the clear regulatory requirement (**21 CFR 211.160(b)(2)**) that all samples sampled and tested must be a *representative sample* from the batch (as "*Representative sample*" is defined in **21 CFR 210.3(b)(21)**) as well as the requirement that all test procedures be *scientifically sound* and *appropriate* (**21 CFR 211.160(b)**. Since the Draft is clearly limited to assessing the uniformity of only one aspect of the in-process materials at only two in-process phases instead of all significant in-process phases, the Draft's title and scope should make it clear that the guidance being provided is ONLY applicable to assessing the uniformity of the active ingredient(s), "**strength**," at only the "final blend" and the "formed dosage unit" phase and not assessing the uniformity of the "**quality**," or "**purity**" of the "**in-process materials, …, and drug products**" "**during the production process**" at all in-process "**significant phases**" (**21 CFR 211.110(c)**) as the CGMP regulations clearly require and the current title and scope of the Draft seem to indicate the draft's guidance addresses. Finally, this reviewer notes that this draft guidance fails to address the clear requirement that each batch of in-process material must be "**approved or rejected by the quality control unit, during the production process**" at the "**commencement or completion of significant phases**" – this requirement should not be ignored or "left in limbo" as the Draft's silence chooses to do.	(Continued) **21 CFR 211.160(b)(2)**, "Laboratory controls shall include the establishment of *scientifically sound* and *appropriate* specifications, standards, sampling plans, and *test procedures* designed to **assure that** components, drug product containers, closures**, in-process materials**, labeling, and **drug products conform to appropriate standards of identity, strength, quality**, and **purity**. Laboratory controls shall include: (1) … . (2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such **samples shall be representative** and properly identified. **21 CFR 210.3(b)(21)**, "***Representative sample* means a sample that consists of a number of units that** are drawn based on rational criteria such as random sampling and intended to **assure that the sample accurately portrays the material being sampled**." **21 CFR 211.110(c)**, "**In-process materials shall be tested for identity, strength, quality, and purity** as appropriate, **and approved or rejected by the quality control unit, during the production process**, e.g., **at commencement or completion of significant phases** or after storage for long periods."
VII - A 337	In addition to the amendment text, please consider adding another bullet: "Previous routine was per SCM and passed SCM criteria." This reviewer agrees that, were the scenarios presented CGMP compliant, this bullet would need to be added. However, factually, the scenarios presented are neither CGMP compliant nor properly address the *scientifically sound* and *appropriate* assessment of even the uniformity of the active(s) in in-process materials and the drug product. On the pages which follow, this reviewer offers a scientifically sound and CGMP-compliant inspection plan for a simple drug product that contains a single active:	Three scenarios to use SCM exist in the PQRI document: 1. validation was readily pass and we are just starting production 2. routine test method is SCM and we continue this as long as we keep passing 3. routine method is MCM, but switching rule is met. Factually, none of the PQRI's scenarios are either *scientifically sound* or *appropriate*. Their scenarios do not take samples that are *representative* of the *batch*. Their scenarios do not even reference, *much less conform to*, the applicable consensus standards for assessing the uniformity of units (*ISO 3951* or *ANSI Z1.9*). Their scenarios are not CGMP compliant.

Section/ Line(s)	Reviewer's Observation | Reviewer's Basis
VII. "337" (Continued)	(Continued) To address the clear CGMP requirement ***minimums*** for the assessment of the uniformity of the active or actives in the final blend and the dosage units formed therefrom, this reviewer offers the following scenario based on the reviewer's observations and basis statements in the preceding Rows and, where they are important, his remarks on this Draft in the prior submissions this reviewer has made to Public Docket 2003D-0493 [**Note:** The plans proposed here do not explicitly address the generally inapplicable "process variability known" situation.]: **Basis Scenario:** Before any comprehensive inspection plan can be proposed, the manufacturing scenario must be clearly delineated because the appropriateness of the inspection plan proposed depends upon the manufacturing scenario under which the drug product is produced. This reviewer will use the following "Example Inspection Plan" for active uniformity in the "final blend" and the "formed dosage units" (both capsules and tablets) to illustrate a comprehensive approach to the inspection of such materials: **Example Inspection Plan For XYZ Pharmaceutical's YZWU Drug Product** XYZ Pharmaceutical is in the process of starting up a **dedicated** manufacturing unit for the continual production of 2-million-dosage-unit batches of a new fast-tracked antiviral drug product, YZWU, which contains a single active, Zwut, which is produced in both tablet and capsule form from the same blends. The process development has proceeded to the point that one (1) scale up batch, one near-full-scale demonstration conformance batch, and three (3) initial full-scale process "evaluation qualification" (EQ) conformance batches have been intensively studied and found to be acceptable and easily meet the *scientifically sound* and *appropriate statistics-based sample specifications* and *batch acceptance criteria* established by the manufacturer, and the firm has produced an additional eight (8) production-scale batches to build inventory. Based on the body of knowledge accumulated, the validity of the inspection sampling plans and the inspection sample testing plans have been established in development and their validity has been confirmed by the results found for the conformance batches. Using those findings, the basis decision variables for active uniformity were defined as follows: **1.** Campaign Manufacture Interruption Switch ("CMI") variable was set to "zero" because there had not yet been any manufacturing interruption or campaign termination. [Decision Points: If CMI = 0, take no action. If CMI = 1, set all switches as follows: (CAB = 0, IBS= "value at last batch produced," IDUS = "value at last batch produced," CRB = "value at last batch produced." **2.** Consecutively Acceptable Batches ("CAB") variable was set to "10" initially for the ten (10) successful EQ conformance and inventory building batches – the Consecutively Non-acceptable Batches ("CNB") variable was set to "zero." [Decision Points: If CRB = 5, STOP manufacture. If CAB < 5, make no decision; when CAB ≥ 5, check to see if a reduction in inspection is supportable. When CAB = 30, consider switch to a "process variability known" ("PVK") plan.] **3.** Blend Inspection Level ("IBS") set to "1" (reduced set) because the data from full-set sampling on all previous batches established that XYZ's reduced sampling plan adequately characterized the final blends. **4.** Dosage-Unit Inspection Level ("IDUS") was set to "2" (normal inspection) since an insufficient body of knowledge had been accumulated to reduce the level of inspection ("IDUS" = 1) and no need had been found to switch to the distribution acceptance set ("IDUS" = 3). **5.** Blend Uniformity Exception ("IBUE") was set to "0" (all previous had met expectations). [Decision Points: "IBUE" > 3, "increase" IDUS; otherwise leave where it is – IDUS reduced one level when CRB = 0 and CAB ≥ 5.] **6.** Drug-Unit Exception ("IDUE") was set to "0" (all precious had met expectations). [Decision Points: "IDUE" >3, "increase" IDUS if less than 3; otherwise leave alone – if IDUS >1 reduced each time CRB =0 and CAB found to be ≥ 5.]

Section/ Line(s)	Reviewer's Observation | Reviewer's Basis
VII. "337" (Continued)	(Continued) **A. INSPECTION OF FINAL BLENDS FOR ACTIVE UNIFORMITY** (Follow "IBS") **1.** Sample, collect, transport, and control the *full batch-representative* set (*established in process development and scale up, and confirmed in at least one near-full-scale conformance batch produced in the "same" [blender configuration and manufacturer] blender as will be used in routine production*) of samples using your established batch-spanning plan that has been proven to collect non-biased samples (each consisting of more than enough material in amount for all possible evaluations for all critical variable factors that must be evaluated for uniformity) in a manner that preserves the link between the sample and the location from which it was sampled. PROCEED as directed by your current value for "IBS." **2.** **BLEND SAGE 1** ("IBS = 1")**:** Select the *minimum batch-representative* subset set (*established based on your analysis of the outcomes from your scale up conformance batches and near-full-scale batches*) and, *using aliquot-removal techniques that have been proven to be capable of sampling unbiased aliquots from your samples*, remove, transfer, weigh, prepare, and test the appropriate number of aliquots from each sample in the sub set in a manner that preserves the link between the location, weight, aliquot ID, and record all the results found along with their identifying information for the active(s) evaluated. PROCEED to **Step 3**. [**Note:** In general, not less than 30 % of the samples should be evaluated in duplicate.] **3.** **BLEND EVALUATION 1:** EVALUATE valid results found and PROCEED as follows: **a.** IF any result is less than 75.0 % or more than 125. % of the targeted level for that blend ("75.0 to 125."), **REJECT** Final Blend, SET "CAB" to "0" (zero), INCREMENT "CRB" and "IBUE," NOTIFY your quality unit, AND PROCEED to **Step b**; ELSE GO to **Step d**. **b.** SET "IBS" to "2" AND PROCEED to **Step c**. **c.** IF "CRB" is greater than 2, SET "CAB" = "0" and "CRB" = "0" AND **STOP** manufacturing Blends until notified to restart production. ELSE sample and test the next Final Blend ("**A**"). **d.** IF the Mean found is within 1 % of the Targeted Mean, PROCEED to **Step e**; ELSE GO to **BLEND STAGE 2 (Step 4**). **e.** IF one (for tablet products) is, or two (for capsule products) are, outside of the range from 87.0 % to 113. % of the targeted level for the Blend, *WHEN "CRB" >0 AND "IBS" = "1",* SET "IBS" to "2" and "IBUE" to "0", AND PROCEED to **BLEND STAGE 2** (**Step 4**). ELSE GO to **Step f**. **f.** IF all results are inside of the range from "87.0 to 113. %" of the target BUT not inside of the range from "90.0% to 110.%" of the target, EITHER, *WHEN 'CRB" = "0" (zero)*, INCREMENT "IBUE" (Blend Uniformity Exception) twice, INCREMENT "CAB," **ACCEPT** the blend for further processing, AND GO to **Step i**, OR, *WHEN CRB > "0" (zero)*, SET "IBS" to 2 AND GO to **BLEND STAGE 2** (**Step 4**). ELSE GO to **Step g**. **g.** IF all of the results are inside of the range from "90.0 to 110. %" of the target BUT not *appropriately* inside of the range from "95.0% to 105.%" of the target, EITHER, *WHEN 'CRB" = "0" (zero)*), INCREMENT "IBUE" and "CAB" once, **ACCEPT** the blend for further processing, AND GO to **Step i**), OR, *WHEN CRB > "0" (zero)*, SET "IBS" to 2, AND PROCEED to **BLEND STAGE 2** (**Step 4**). ELSE GO to **Step h** **h.** IF all of the results are *appropriately* inside of the range from "95.0 to 105. %" of the target, INCREMENT "CAB," AND **ACCEPT** the blend for further processing. PROCEED to **Step i**. **i.** IF "IBUE" > "3," *UNLESS "IDUS" = "3"*, INCREMENT "IDUS," SET "IBUE" to "0" (zero), AND GO to **Step j**. ELSE just GO to **Step j**. **j.** IF "CAB" ≥ "5," SET "CRB" to "0" (zero), PROCEED to sample and test the next Final Blend ("**A**"). ELSE just GO to "**A**"

Section/ Line(s)	Reviewer's Observation | Reviewer's Basis
VII. "337" (Continued)	(Continued) **4. BLEND STAGE 2** ("IBS" = 2)**:** *For the samples not previously sampled*, using aliquot-removal techniques that have been proven to be capable of sampling unbiased aliquots form your samples, remove, transfer, weigh, prepare, and test duplicate aliquots from each sample in the subset in a manner that preserves the link between the location, weight, aliquot ID, and valid results found for the active(s). *For the previously tested samples*, evaluate a single additional aliquot from each of these samples both to obtain within-location estimates of active level where the previous location samples were only sampled and evaluated in singlicate and, where the location samples were previously evaluated in duplicate, provide some estimate of the bias, if any, between the test sets (the original and the current one). Conduct this Step in the same manner as discussed for **BLEND STAGE 1**. PROCEED to **Step 5**. **5. BLEND EVALUATION 2:** EVALUATE valid results and PROCEED as follows: **a.** IF any result is less than 75.0 % or more than 125. % of the targeted level for that blend OR the mean observed is not within 1 % of the targeted mean, REJECT the blend, SET "CAB" = 0, INCREMENT "CRB" once and "IBUE" 3 times, NOTIFY your quality unit, AND GO to **Step b**. ELSE GO to **Step c**. **b.** IF "CRB" is greater than 2, SET "CAB" = "0" and "CRB" = "0" AND **STOP** manufacturing Blends until notified to restart production. ELSE sample and test the next Final Blend ("**A**"). **c.** IF none are less than 80.0 % of the target, BUT more than 1 (for tablet products) result is, or more than 2 (for capsules), results are outside of the range from 85.0 % to 115. % of the targeted level for the Final Blend, REJECT the Blend, NOTIFY your quality unit, AND GO to **Step b**. ELSE GO to **Step d**. **d.** IF all results are in the range from "85.0 to 115. %" of the target, BUT 2 (for tablet products) [or 3 (for capsule products)] are outside of the range from "87.0 % to 113. %" of the target, INCREMENT "IBUE" twice, INCREMENT "CAB," ACCEPT the blend for further processing, AND PROCEED to **Step g**. ELSE GO to **Step e**. **e.** IF all results are inside of the range from "87.0 to 113.%" of the target BUT not inside of the range from "92.0 % to 108. %" of the target, THEN, INCREMENT "CAB" and "IBUE" once, ACCEPT the blend for further processing, AND GO to **Step g**; ELSE PROCEED to **Step f**. **f.** IF all of the results are inside of the range from "92.0 to 108. %" of the target, INCREMENT "CAB," ACCEPT the blend for further processing, AND GO to **Step g**. **g.** IF "IBUE" > "3," *UNLESS "IDUS" = "3"*, INCREMENT "IDUS," SET "IBUE" to "0" (zero), AND GO to **Step h**. ELSE GO to **Step h**. **h.** IF "CRB =0, "CAB" ≥ 5, "IBUE" = 0 and "IBS" = 2, SET "IBS" to "1," AND GO to **Step i**. ELSE, just GO to **Step i**. **i.** IF "CAB" ≥ "5," SET "CRB" to "0" (zero), AND PROCEED to sample and test next Final Blend ("**A**"). ELSE just GO to "**A**."

Section/ Line(s)	Reviewer's Observation | Reviewer's Basis
VII. "337" (Continued)	(Continued) **B. INSPECTION OF DOSAGE UNITS FOR ACTIVE UNIFORMITY** (Follow "IDUS") **1.** Sample, collect, transport, and control the *full batch-representative* set (*established in process development and scale up, and confirmed in at least one near-full-scale conformance batch produced in the "same" [equipment operating conditions and configuration, and manufacturer] dosage-forming equipment as will be used in routine production*) of samples using your established batch-spanning plan that has been proven to collect non-biased *sampling-point-representative samples* (each consisting of some integer multiple of the number of dosage-forming stations in the equipment being used [to ensure each sample is representative of the "local" production environment at the time of the sampling]) at each sampling point subject to the constraint that the total number collected is batch-representative and more than enough dosage units in number for all possible evaluations for all critical variable factors that must be evaluated for uniformity) in a manner that preserves the link between the sample and the sampling point from which it was sampled. THEN, *based on the Stage established when the final blend was accepted*, PROCEED to the Appropriate DOSAGE UNIT STAGE (controlled by current "IDUS" value). **2.** **DOSAGE-UNIT STAGE 1** ("IDUS = 1)**:** For the set of sampling points defined in your established DOSAGE-UNIT INSPECTION PLAN, SELECT ***not less than* 50 dosage units** *at random* from the set of sampling points at which sample units were collected subject to the constraint that an equal number of dosage units should be collected *at random* from each "routine" sampling point. The sample collection should be done in a manner that preserves the relationship between each sampling point and the samples chosen at that point. For each dosage unit that has been selected, weigh, prepare, and test each dosage sample in a manner that preserves the link between the sampling point, weight, dosage unit "ID," acquire the valid results found for the active(s) in each dosage unit tested, and record all the results found along with their identifying information for the active(s) evaluated. PROCEED to **Step 3**. [**Note:** In general, unless the test system produces result values that are the average of multiple readings, all of the sample preparations should be evaluated in duplicate. Even in such "test-equipment averaged" cases, not less than 10 % should be evaluated in duplicate. Moreover, the order of evaluation should be completely randomized.] **3.** **DOSAGE UNIT EVALUATION 1:** EVALUATE valid results found and proceed as follows: **a.** IF any result is less than 75.0 % or more than 125. % of the targeted level for the formed dosage units ("75.0 to 125. %") OR more than 2 (for tablets) or 3 (for capsules) are outside of the range from "85.0 to 115. %" of the target, REJECT the dosage unit batch, SET "CAB" to "0," INCREMENT "CRB" once and "IDUE" 3 times, NOTIFY your quality unit AND GO to **Step b**. ELSE GO to **Step c**. **b.** IF "CRB" is greater than 2, **STOP** manufacturing dosage-form batches until notified to restart production. ELSE sample and test the next Final Blend ("**A**"). **c.** IF the Mean found is within 1 % of the Targeted Mean, PROCEED to **Step d**; ELSE, GO to **DOSAGE-UNIT STAGE 2** (**Step 4**) **d.** IF 1 (for tablets) is, or 2 (for capsules) are, outside of the range from 85.0 % to 115. % of the targeted level for the formed dosage units, EITHER, *WHEN 'CRB" = "0" (zero)*), PROCEED to **DOSAGE-UNIT STAGE 2** (**Step 4**) OR, *WHEN CRB > "0" (zero)*, REFER the batch to your quality unit for their decision (IF ACCEPT, SET "IDUS" to "2" AND GO to **Step f**. IF REJECT, SET "CAB" to "0," INCREMENT "CRB," AND GO to **Step e**.) ELSE, GO to **Step f**. **e.** IF "CRB" > 2, STOP manufacturing dosage-form batches until notified to restart production, AND SET "IDUE" = "0." ELSE, INSPECT next "Dosage Units" Batch ["**B**"]).

Section/ Line(s)	Reviewer's Observation | Reviewer's Basis
VII. "337" (Continued)	(Continued) **f.** IF all results are inside of the range from "85.0 to 115." of the target BUT not inside of the range from "92.0 to 108. %" of the target, EITHER, *WHEN 'CRB" = "0" (zero)*), EVALUATE results using your proven AQL (% Nonconforming), your ISO/ANSI *reduced*-inspection "process variability unknown—SD" plan, ACCEPT the batch when the data meets the ISO/ANSI acceptance criteria, INCREMENT "CAB" once and "IDUE" twice, AND GO to **Step i**. OR, *WHEN "CRB" > 0 OR data does NOT MEET ISO/ANSI criteria*, PROCEED to **DOSAGE STAGE 2**(**Step 4**) *when not more than 1 (for tablets) or 2 (for capsules) is outside of "90.0 % to 110. % of target* OR, *when not more than 4 (for tablets) or 6 (for capsules) are outside of "92.0 to 108. %" of the target*, PROCEED to **DOSAGE-UNIT STAGE 3** (**Step 6**). ELSE, GO to **Step g**. **g.** IF all of the results are inside of the range from "92.0 to 108." of the target BUT not inside of the range from "95.0% to 105. %" dosage units, EITHER, *WHEN 'CRB" = "0" (zero)*), EVALUATE the results using your proven AQL (% Nonconforming), your ISO/ANSI reduced-inspection "process variability unknown—SD" plan, ACCEPT the batch when the data meets the ISO/ANSI acceptance criteria, INCREMENT "CAB" and "IDUE," AND GO to **Step i**. OR, *WHEN "CRB" > 0, OR data does NOT MEET ISO/ANSI criteria*, DO NOT INCREMENT any counters, AND PROCEED to **DOSAGE STAGE 2** (**Step 4**). ELSE, GO to **Step h**. **h.** IF all of the results are inside of the range from "95.0 to 105." of the target, EVALUATE the results using your proven AQL (% Nonconforming) and your ISO/ANSI reduced-inspection "process variability unknown—SD" plan, ACCEPT the batch when the data meets the ISO/ANSI acceptance criteria, INCREMENT "CAB" AND GO to **Step i**. **OR**, *WHEN data does not meet criteria*, PROCEED to **DOSAGE STAGE 2** (**Step 4**). **i.** IF "IDUE" > "3," *UNLESS "IDUS" > "2"*, INCREMENT "IDUS," SET "IDUE" to "0" (zero), AND GO to **Step j**. ELSE GO to **Step j**. **j.** IF "CRB =0, "CAB" ≥ 5, "IBUE" = 0 and "IDUS" = 2, SET "IDUS" to "1," AND GO to **Step k**. ELSE, just GO to **Step k**. **k.** IF "CAB" ≥ "5," SET "CRB" to "0" (zero), AND PROCEED to sample and test next dosage-unit batch ("**A**"). ELSE GO to "**A**." **4. DOSAGE-UNIT STAGE 2** ("IDUS" = 2)**:** For the set of sampling points defined in your established DOSAGE-UNIT INSPECTION PLAN, SELECT **not less than** "**200**"[1] **dosage units** *at random* from the set of sampling points at which sample units were collected subject to the constraint that an equal number of dosage units should be collected *at random* from each "routine" sampling point. The sample collection should be done in a manner that preserves the relationship between each sampling point and the samples chosen at that point. For each dosage unit that has been selected, weigh, prepare, and test each dosage sample in a manner that preserves the link between the sampling point, weight, dosage unit "ID," acquire the valid results found for the active(s) in each dosage unit tested, and record all the results found along with their identifying information for the active(s) evaluated. PROCEED to **Step 5**. [**Note:** In general, unless the test system produces result values that are the average of multiple readings, all of the sample preparations should be evaluated in duplicate. Even in such "test-equipment averaged" cases, not less than 10 % should be evaluated in duplicate. Moreover, the order of evaluation should be completely randomized.] [1] In cases where 50 representative units have already been evaluated, you need only select an additional 150 batch-representative dosage-unit samples.

Section/ Line(s)	Reviewer's Observation | Reviewer's Basis
VII. "337" (Continued)	(Continued) **5. DOSAGE-UNIT EVALUATION 2:** EVALUATE the valid results found and proceed as follows: **a.** IF any result is less than 75.0 % or more than 125. % of the targeted level for the formed dosage units, OR more than 5 (for tablets) or 9 (for capsules) are outside of the range from "85.0 to 115. %" of the target, REJECT the dosage-unit batch, SET CAB to "0," INCREMENT "CRB" once and "IDUE" 3 times, NOTIFY your quality unit, AND GO to **Step b**. ELSE GO to **Step c**. **b.** IF "CRB" is greater than 2, **STOP** manufacturing Blends until notified to restart production; ELSE sample and test the next batch of dosage units ("**B**"). **c.** IF the Mean found is within 0.5 % of the Targeted Mean, PROCEED to **Step d**; ELSE, GO to **DOSAGE-UNIT STAGE 3**. **d.** IF 3 (for tablets) is, or 6 (for capsules) are, outside of the range from 85.0 % to 115. % of the targeted level for the formed dosage units, EITHER, *WHEN 'CRB" = "0" (zero)*), GO to **DOSAGE-UNIT STAGE 3** (**Step 6**) OR, *WHEN CRB > "0" (zero)*, REFER the batch to your quality unit for their decision (IF ACCEPT, SET "IDUS" to "3" AND GO to **Step f**. IF REJECT, SET "CAB" to "0," INCREMENT "CRB," AND GO to **Step e**.) ELSE, GO to **Step f**. **e.** IF "CRB" > 2, STOP manufacturing dosage-form batches until notified to restart production, AND SET "IDUE" = "0." ELSE, INSPECT next "Dosage Units" Batch ["**B**"]. **f.** IF all results are inside of the range from "85.0 to 115." of the target BUT not inside of the range from "92.0 to 108. %" of the target, EITHER, *WHEN 'CRB" = "0" (zero)***)**, EVALUATE results using your proven AQL (% Nonconforming), your ISO/ANSI *reduced*-inspection "process variability unknown—SD" plan, ACCEPT the batch when the data meets the ISO/ANSI acceptance criteria, INCREMENT "CAB" once and "IDUE" twice, AND GO to **Step i**. OR, *WHEN "CRB" > 0 OR data does NOT MEET ISO/ANSI criteria*, PROCEED to **DOSAGE STAGE 3**(**Step 6**). ELSE, GO to **Step g**. **g.** IF all of the results are inside of the range from "92.0 to 108." of the target BUT not inside of the range from "95.0% to 105. %" dosage units, EITHER, *WHEN 'CRB" = "0" (zero)***)**, EVALUATE the results using your proven AQL (% Nonconforming), your ISO/ANSI reduced-inspection "process variability unknown—SD" plan, ACCEPT the batch when the data meets the ISO/ANSI acceptance criteria, INCREMENT "CAB" and "IDUE," AND GO to **Step i**. OR, *WHEN "CRB" > 0, OR data does NOT MEET ISO/ANSI criteria*, DO NOT INCREMENT any counters, AND PROCEED to **DOSAGE STAGE 3** (**Step 6**). ELSE, GO to **Step h**. **h.** IF all of the results are inside of the range from "95.0 to 105." of the target, EVALUATE the results using your proven AQL (% Nonconforming) and your ISO/ANSI reduced-inspection "process variability unknown—SD" plan, ACCEPT the batch when the data meets the ISO/ANSI acceptance criteria, INCREMENT "CAB" AND GO to **Step i**. **OR**, *WHEN data does not meet ISO/ANSI criteria*, PROCEED to **DOSAGE STAGE 3** (**Step 6**). **i.** IF "IDUE" > "3," *UNLESS "IDUS" > "3"*, INCREMENT "IDUS," SET "IDUE" to "0" (zero), AND GO to **Step j**. ELSE GO to **Step j**. **j.** IF "CRB =0, "CAB" ≥ 5, "IDUE" = 0 and "IDUS" = 2, SET "IDUS" to "1," AND GO to **Step k**. ELSE, just GO to **Step k**. **k.** IF "CAB" ≥ "5," SET "CRB" to "0" (zero), AND PROCEED to sample and test next dosage-unit batch ("**A**"). ELSE GO to "**A**."

Section/ Line(s)	Reviewer's Observation | Reviewer's Basis
VII. "337" (Continued)	(Continued) **6. DOSAGE-UNIT STAGE 3** ("IDUS" = 3)**:** For the set of sampling points defined in your established DOSAGE-UNIT INSPECTION PLAN, SELECT **not less than "400"[1] dosage units** *at random* from the set of sampling points at which sample units were collected subject to the constraint that an equal number of dosage units should be collected *at random* from each "routine" sampling point. The sample collection should be done in a manner that preserves the relationship between each sampling point and the samples chosen at that point. For each dosage unit that has been selected, weigh, prepare, and test each dosage sample in a manner that preserves the link between the sampling point, weight, dosage unit "ID," acquire the valid results found for the active(s) in each dosage unit tested, and record all the results found along with their identifying information for the active(s) evaluated. PROCEED to **Step 5**. [**Note:** In general, unless the test system produces result values that are the average of multiple readings, all of the sample preparations should be evaluated in duplicate. Even in such "test-equipment averaged" cases, not less than 10 % should be evaluated in duplicate. Moreover, the order of evaluation should be completely randomized.] [1] In cases where 200 representative units have already been evaluated, you need only select an additional 200 batch-representative dosage-unit samples. **7. DOSAGE-UNIT EVALUATION 2:** EVALUATE the valid results found and proceed as follows: **a.** IF any result is less than 75.0 % or more than 125. % of the targeted level for the formed dosage units ("75.0 to 125. %") OR more than 12 (for tablets) or 21 (for capsules) are outside of the range from "85.0 to 115. %" of the target, REJECT the dosage unit batch, SET CAB to "0," INCREMENT "CRB" once and "IDUE" 3 times, NOTIFY your quality unit, AND GO to **Step b**. ELSE GO to **Step c**. **b.** IF "CRB" is greater than 2, **STOP** manufacturing Blends until notified to restart production; ELSE sample and test the next batch of dosage units ("**B**"). **c.** IF the Mean found is within 0.3 % of the Targeted Mean, PROCEED to **Step d**; ELSE, REFER the formed dosage-units batch to your quality unit. **d.** IF all results are inside of the range from "85.0 to 115. %" of the target BUT not inside of the range from "90.0 to 110. %" of the target, EVALUATE the results using the criterion: **{The lesser of |115. – $\bar{x}$| or |$\bar{x}$ – 85.0|} divided by (3.27 x RSD $_{n=400}$) is ≥ 1.5**, AND ACCEPT the batch as having an acceptable active uniformity when the data meets that criterion, INCREMENT "CAB," AND GO to **Step f.** OR, *WHEN the data does not meet this criterion*, EITHER REJECT the dosage-units batch, SET "CAB" = "0," INCREMENT "CRB" once AND "IDUE" twice, START an investigation AND PROCEED to **Step e**. OR REFER the batch to your quality unit for handling. [**Note:** Your choice here should be based on the previous history ("CRB") for the formed dosage units of this drug product.] ELSE, GO to **Step f**. **e.** IF "CRB" > 2, **STOP** manufacturing dosage-form batches until notified to restart production, AND SET "IDUE" = "0." ELSE, INSPECT next "Dosage Units" Batch ["**B**"]. **f.** IF all of the results are inside of the range from "90.0 to 110." of the target BUT not inside of the range from "95.0% to 105. %" of the target for the dosage units, EVALUATE the results using the criterion: **{The lesser of |115. – $\bar{x}$| or |$\bar{x}$ – 85.0|} divided by (3.27 x RSD $_{n=400}$) is ≥ 1.8**, AND ACCEPT the batch as having an acceptable active uniformity when the data meets that criterion, INCREMENT "CAB," AND GO to **Step h**. OR, WHEN it does not, EVALUATE using the previous criterion: **{The lesser of |115. – $\bar{x}$| or |$\bar{x}$ – 85.0|} divided by (3.27 x RSD $_{n=400}$) is ≥ 1.5**, AND ACCEPT the batch as having an acceptable active uniformity when the data meets that criterion, INCREMENT "CAB" and "IDUE," AND, GO to **Step h**. OR, *WHEN it dose not meet this relaxed criterion*, REFER the batch to your quality unit for exception handling.

Section/ Line(s)	Reviewer's Observation | Reviewer's Basis
VII. "337" (Continued)	(Continued) **g.** IF all of the results are inside of the range from "95.0 to 105." of the target, EVALUATE the results using the criterion: **{The lesser of |115. – $\bar{x}$| or |$\bar{x}$ – 85.0|} divided by (3.27 x RSD $_{n=400}$) is ≥ 2.0**, AND ACCEPT the batch as having an acceptable active uniformity when the data meets that criterion, INCREMENT "CAB," AND GO to **Step h**. OR, WHEN it does not, EVALUATE using the previous criterion: **{The lesser of |115. – $\bar{x}$| or |$\bar{x}$ – 85.0|} divided by (3.27 x RSD $_{n=400}$) is ≥ 1.8**, AND ACCEPT the batch as having an acceptable active uniformity when the data meets that criterion, INCREMENT "CAB" and "IDUE," AND, GO to **Step h**. OR, *WHEN it dose not meet this relaxed criterion*, REFER the batch to your quality unit for exception handling. **h.** IF "CRB =0, "CAB" ≥ 5, "IDUE" = 0 and "IDUS" = 3, SET "IDUS" to "2," AND GO to **Step i**. ELSE, just GO to **Step i**. **i.** IF "CAB" ≥ "5," SET "CRB" to "0" (zero), AND PROCEED to sample and test next dosage-unit batch ("**B**"). ELSE GO to "**B**." **[Nota Bene:** The dosage-unit inspection plans proposed for the are based on those applicable consensus (ISO, ANSI) standard's "process variability unknown—standard deviation" plans for Stage I and Stage 2 and a distribution statistics criterion for the Stage 3. The consensus standard's "process variability unknown" plans must be used until: **i.** The drug product's history encompasses a sufficient number (typically, not less than 15+) of consecutive acceptable batches indicates that the process is capable of operating in control for significant periods of time and, if any, the root causes of any non-complying batches have been conclusively identified, **ii.** The observed mean and variability for the accepted batches both fall in a narrow range, and **iii.** The controls on the acceptance of all components a. **Fully comply with all** the applicable **CGMP** requirement ***minimums***. b. **Have been proven to include sufficiently rigorously controls on all** critical physical and chemical characteristics for all components. c. **Historically indicate that**, *when any non-conformance of an in-process material has been traced to or implicated the controls on a component*, the **controls** on that component **have been *appropriately* strengthened**. d. **Retrospective treatment of the results data using** the current apparent **RSD $_{Process}$ for all batches**, ***including those that were not released***, as an approximation for the process variability **$\sigma_{Process}$ and** the ***applicable*** ISO or ANSI consensus **standard's "process variability known" plans does NOT change the release status of any released or rejected batch**. When all of the preceding condition have been met, you may consider changing your "Stage 1" and "Stage 2" plans to the corresponding, "process variability known" ISO or ANSI consensus standards' "**Stage A**" and "**Stage B**" plans mentioned by this reviewer that, in general terms, reduce the "REDUCED" inspection plan from "50" representative dosage units to on the order of "12 – 22" for AQL's not greater than 1.5 % and, for the "NORMAL" inspection plans, from "200" *representative dosage units* to on the order of "40 to 70" for AQL's not greater than 1.5 %. {**Note:** Given the **USP**'s post-release, in commerce expectations, a manufacturer would have a hard time justifying an AQL for active content that is greater than 1.5 % for tablets (4.0 % for capsules).}**]** Hopefully, the Agency will review this example plan and find that, *unlike the plan in the Draft*, find that this plan is, at the 95 % confidence level, a *scientifically sound* statistics-based plan that meets the CGMP's clear in-process ***minimums*** for assessing the *uniformity of the active* in *final blends* and the *formed dosage units*.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VII. A.2 "348"	We suggest adding a footnote as follow: (3) weight correct [17] [17] Allow for the option of not weight correcting the stratified unit dose data during routine batch manufacture." The Draft's proposal is at odds with the clear in-process CGMP requirement to monitor the characteristic "active level" in the dosage units (and not some adjusted characteristic as these commenter's propose here). No footnote should be added; instead, the Draft's "(3) weight correct" should either be removed or restated as "(3) weight correct *only for the purposes of comparing the distribution of the weight-corrected dosage-unit data to the distribution of the blend data*"	Using non-weight corrected data to pass routine manufacturing criteria is more stringent, but it allows for only one set of calculations to pass both routine criteria and the content uniformity test Factually, to meet the clear in-process CGMP "characteristics" monitoring requirements **of 21 CFR 211.110(a)**, the "as is" active level data must be used to determine the uniformity of the batch of dosage units with respect to its active level. Obviously, the text here does not conform the clear requirements of the applicable regulation here and, *because the FDA's guidance is required by law to conform to clear regulations*, the draft needs to be appropriately corrected.
VII. A.2. "361-363"	We suggest adding "weight corrected" to this sentence: "To perform the stage 2 test, we recommend that you assay the remaining two dosage units (from stage 1) for each sampling location and compute the mean and RSD of the weighted corrected [17] data combined from both stage 1 and stage 2." The Draft's proposal is at odds with the clear in-process CGMP requirement "to monitor the characteristic "active level" in the dosage units (and not some adjusted characteristic) as these commenter's propose here. The change suggested should not be made.	Using non-weight corrected data to pass routine manufacturing criteria is more stringent, but it allows for only one set of calculations to pass both routine criteria and the content uniformity test Factually, to meet the clear in-process CGMP "characteristics" monitoring requirements of **21 CFR 211.110(a)**, the "as is" data must be used to determine the uniformity of the batch of dosage units with respect to its active level. Clearly, the text here does not conform the clear requirements of the applicable regulation here and, *because the FDA's guidance is required by law to conform to any clear regulation*, the draft needs to be appropriately corrected.
VII - B "382"	In addition to the amendment text, please consider adding another bullet: "Previous routine test used MCM and passed MCM criteria" Though the commenter's suggestion is logically correct, this reviewer cannot support it because the entire Inspection Plan proposed in the Draft is neither CGMP compliant nor *scientifically sound*.	Three scenarios to use MCM exist in the PQRI document: 1. validation was marginally pass and we are just starting production 2. routine test method is MCM and we continue this until we can switch 3. last batch used SCM, but had to go to MCM to pass. This reviewer notes that FDA guidance is supposed to be CGMP compliant and *scientifically sound* – the PQRI document and the published Draft are neither.
VII. C. "401" Table of Contents	Please consider using "Criteria" instead of "Test" as in "Switching to the Standard Criteria Method (SCM) from Marginal Criteria Method (MCM)." (Note this is also in the Table of Contents) This reviewer agrees that the terminology within any scientific document should be consistent and accurate.	The MCM and SCM terminology used need to be consistent within the guidance document.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VII - C "404"	We suggest revising "… criteria and result in RSD …" to "criteria and for each batch the RSD …" If the purpose of the clarification were simply to clarify this proposed requirement in a *scientifically sound* and grammatically correct manner as the commenter's remarks seem to indicate, then this reviewer suggest that it be rewritten: "• Five consecutive batches pass the MCM criteria and each passing batch has a sample RSD ≤ 5.0 %" However, this reviewer would be remiss if he did not point out that the criteria proposed do not comply with CGMP and, in addition, are patently insufficient and deficient upon their face.	. This has currently been misread that all batches are combined together to get the RSD. The change would clarify that each batch RSD must meet this. Even if you ignore the clear requirement minimums of **21 CFR 211.165(d)** and incorrectly believe that the **USP** criteria are controlling, the key criterion in most cases is the number allowed outside of 85 to 115 % of the target (e.g., 1 in any 30 for tablets) and not the RSD per se. Lacking a proper "mean" specification that ensures the batch meets the "provide not less than 100 percent of the labeled or established amount of active ingredient" of **21 CFR 211.101(a)**, it is easy for a set of data centered about a mean of "95 %" that has an RSD of 5.0 (which on its face translates into units in the batch between 66 % to 126 %) that: a) Clearly has units below 75 % and more than 2 % of its units may have values below 85 % making it almost certain that some "articles" will have more than 1 in 30 below 85 % - and, if tested after release, such released batches will fail.
VIII "416"	We suggest revising this sentence to read: "We recommend that you provide the following information, if available, in the … ." *While this reviewer agrees that the information from the initial full-scale conformance batches produced for the initial process "Performance Qualification" confirmation of process reproducibility may not be available*, to submit an application, the manufacturer is supposed to have fully developed their drug product processes, including production of at least one (1) process conformance demonstration batch, then all the information needed should be available before a submission is filed. Therefore, this reviewer cannot, in good conscience, agree with the commenter's suggestion here unless the commenter's intention is to admit that the industry submits processes that they do not know are valid and well-controlled for FDA review and approval with the hope that, after approval, said production processes may consistently produce acceptable batches that meet the CGMP ***minimums*** with the knowledge that their hope may not be realizable – an apparently clear subversion of the regulatory process.	Most valuable data would be generated from validation batches which most likely are not made at the time of filing. If the commenter truly believes that the "Most valuable data" required to establish the validity of the firm's processes is obtained from the firm's initial "validation batches" but, though the firm knew it needed this "Most valuable data," the commenter's firm is submitting filings lacking this information because the Agency's policy is that such batches can be made after approval. Given the commenter's position and the firm's knowledge of what is needed, it would seem that the Agency should strongly consider revisiting that policy. If needed data is not available, the firms should withhold their filings until such time as the requisite data, including that data required to assess the uniformity of all critical variable factors, including, but most certainly not limited to, active level, is available.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
416,429,436	Please consider consolidating all information provided into a single REGIONAL CTD section. This reviewer does not agree with this recommendation because the guidance places it where the CTD specifies that it be placed. Moreover, the commenter's remarks ignore several realities. First, this reviewer does agree with the commenter that the law in the United States, as interpreted by the regulations and binding FDA policies does require this to information to be available and, in this case, filed for any drug product approved by the US FDA. However, other governments use the US regulations, final Agency guidances, and Agency policies as the basis for their regulations, guidances, and policies. Finally, today's computerized systems make it child's play to "compile, link, and review" the same information into a variety of formats. If other countries using the CTD format do not currently require that the uniformity of their drug products be established in their submissions, they should do so or the Agency should not enter into an MRA with that government's corresponding agency.	Information is spread over different sections of each application, making it difficult to compile, link, and review. As this information is only required in the US, it should be included in the Regional section of the CTD. Under the MRA (**21 CFR 26**), the regulatory control systems used by the US and an covered government that wishes to use the MRA process must have equivalent systems and, if the commenter's remarks are true, then none of these EU candidates should be considered for an equivalence assessment until that government has established that their firms are required to prove their processes produce drug products that are uniform with respect to all of their critical variable factors at each manufacturing phase before the in-process product can be used in the next phase. This document is an example of the ease with which information can be compiled, linked and reviewed even though the reviewer's remarks are spread much more widely (across multiple sections [one for each commenter] each in its own format and with certain topics discussed in different parts of each sections) than in three (3) well-defined sections of the CTD.
VIII.A. "422-423"	We recommend adding unit dose to this sentence: Summary of data analysis from the powder mix assessment and from stratified *unit dose* testing." This reviewer agrees with the commenter that this bullet point needs to be changed to clarify that the analysis must include the data from unit-dose testing. However, this reviewer disagrees with the commenter's suggested language and recommends revising it to read: "• Summary of the data and data analysis from the powder mix assessment ~~and~~ as well as from ~~stratified sample testing~~ the dynamic and static batch-representative sampling, examination, testing, and evaluation of the in-process "freshly formed" dosage units ~~or~~ and the "finished' dosage units to demonstrates compliance with **21 CFR 211.110**, and for the finished drug product, the statistical quality control requirements of **21 CFR 211.165(d)** with respect to the active content, and any other variable factor(such as Dissolution, Drug Release, impurity, water content, residual solvents) that may adversely impact the safety and efficacy of the dosages units in the batch.	This change clarifies that analysis of the stratified unit dose data along with the blend data is needed. While the commenter's rationale is valid on its face, the text needs to provide a more detailed guidance that is linked to the regulatory requirements that apply because, as much of the text in the published Draft and the PQRI's documents indicate, many in the industry seem to be unaware of certain clear CGMP requirement ***minimums***. Moreover, as the Draft's: 1. Only setting specifications whose basis is, at best, unclear as if they were somehow directly applicable to the untested batch, 2. Providing less than *scientifically sound* limits and ranges for the specifications they do set, 3. Failing to provide any valid *batch acceptance criteria*, 4. Failing to even reference, much less, *as they should have*, use the recognized consensus standards (ISO 3951 or ANSI Z1.9) that apply to the inspection of the dosage units in a batch for variable factors, ***clearly*** indicate, the Draft needs to provide guidance that addresses these issues.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VIII.A "423-424"	We recommend changing "demonstrating a normal distribution" to "evaluating the distribution." This reviewer cannot agree with the commenter's suggestion because the alternative proposed, "evaluating the distribution," has no clear meaning since the commenter proposes no criteria against which to evaluate the distribution, does not specify any valid general approach that should be used for "said" evaluation, and, *if read literally*, is, like the oft-used classic "more people climb mountains than in summer," difficult for this reviewer to ascertain what the alternative is meant to state. To address the issues raised, this reviewer suggests the following revision: "• ~~Summary of the stratified~~ An informative tabulation of the results obtained from the in-process batch-representative dosage ~~unit~~ units that were dynamically or statically sampled and tested to support the uniformity of the drug product batches with respect to the active and an analysis of that data which demonstrates the: ~~sampling data analysis demonstrating a~~ a. Degree to which the data approximates a normal distribution of active ingredient and the other components that govern the availability of the active in the batch, b. Validity of the batch release specifications set for the in-process final blend, the "freshly formed" dosage units and the "finished" drug product, and c. Compliance of the sampling and testing of the output of the various in-process manufacturing steps and the finished drug product with the CGMP requirements, as well as the validity of the controls on the incoming components, in-process materials and the drug product.	A normal distribution is acceptable, but not required. Factually, the commenter's statement is, at best, unfocused. The only time a normal distribution has as little importance as the commenter's statement gives it is when distribution-free statistics are used. Mathematically, most of the statistical formulas that this commenter uses fundamentally require that the distribution of the numbers used in them is a near-normal or Gaussian distribution. For practical, real-world use, one can relax the mathematical ideal provided the underlying population is uniform and near enough to normal. If this commenter truly thinks that this guidance should use distribution-free statistics so that the underlying batch distribution is of no concern, then why did this commenter not propose the use of distribution-free approaches? Could it be that the appropriate distribution-free statistical procedures require the testing of as significantly larger number of *batch-representative samples* than the *scientifically sound numbers* required to comply with the CGMP ***minimums***, but not proposed in this Draft? Until this commenter elects to promote the use of such valid distribution-free approaches, let the commenter cease from attempting to deny the reality that a normal distribution of results, or at least a near-normal, uniform distribution of results is required before it is *scientifically sound* and *appropriate* to calculate an RSD using the normal-statistics-based formulas that the commenter uses or recommends.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VIII.A. "426-427"	We suggest revising the sentence to: "Summary of the blend and in-process dosage unit analysis demonstrating that it met the minimum criteria for validation and establishing initial criteria." Though this reviewer agrees with the commenter that this bullet should be revised, this reviewer does not agree with the commenter's rationale and instead suggests changing the Draft to read: "• Summary of the powder mix, in-process formed dosage units and drug product sampling data and a supporting scientifically sound and appropriate batch-statistics-based analysis demonstrating that ~~it~~ both the *batch-representative samples tested from* and *the batch of each material* met the minimum CGMP-compliant in-process statistics-based criteria for the initial process validation and for establishing the validity of the initial criteria used to establish the uniformity of the various materials with respect to the content of the active or actives in said materials and similar analyses should be reported for the other critical variable factors."	Modifying this sentence to include the stratified dosage unit data as there may be sampling errors confounding the blend data. If the commenter's blend-sampling plans use techniques known, as their statement "… may be sampling errors …" indicates, to produce biased samples and "sampling errors," the CGMP regulations require the commenter to change said plans until these biases and error-risks have been eliminated and the commenter's sampling plans become, as required by CGMP for *scientifically sound sampling plans*. Since this reviewer knows from years of experience that the unbiased, error-minimal sampling and testing (inspection) of powder mixes is doable and has overseen the successful performance thereof, this reviewer finds the commenter's remarks a red herring that attempts to focus the Agency on the body of evidence documenting the industry's failure to develop and follow such valid powder-mix inspection plans and procedures rather than, as the Agency should, the manufacturer's absolute duty, under **21 CFR 211.160**, to establish and follow "…**scientifically sound and appropriate** specifications, standards, **sampling plans, and test procedures** designed **to assure that** components, drug product containers, closures, **in-process materials**, labeling, **and drug products conform to appropriate standards of** identity, **strength, quality, and purity.**"
VIII. A. "439-440"	We suggest revising the sentence to: "Summary of data analysis for in-process dosage unit stratified sampling and finished product uniformity of content to support the use pf stratified in-process sample data as an alternative to the USP Content Uniformity Test." This reviewer cannot support the commenter's suggestion because it falsely asserts that the "USP Content Uniformity Test" can validly be used to satisfy the CGMP requirement ***minimums*** (e.g., **21 CFR 211.110**, **21 CFR 211.160**, and **21 CFR 211.165(d)**) for uniformity of the active in the drug product at any stage prior to release Since said **USP** test is patently invalid for use whenever the *sample* must be *batch representative* and the CGMP regulations clearly require all such samples to be *batch representative*, manufacturers who use the "USP Content Uniformity Test" as their batch acceptance/release are clearly releasing batches of drug products that are adulterated by statute (**21 U.S.C. 351(a)(2)(B)**) and the binding regulations (**21 CFR 210.1(b)**).	The original PQRI document showed that stratified samples are more discriminating than finished product samples, therefore it isn't clear what value is added by "validating" the stratified samples by correlating with finished product samples. First, it is, or should be, obvious that the **USP** test is not designed to sample *samples* that are *representative* of even the container they are taken from, much less the batch – said test is, as it must be, a *grab-sample* test – a "take any 30 dosage units" test that totally ignores the representativeness of the sample. In general, these "*any 30 dosage units*," even if *batch representative*, are not a sufficient number for full-scale manufacturing processes producing hundreds of thousands or millions of dosage units without rigorous controls on all the *critical* physical and chemical properties of all of the components in the formulation at a confidence level of 95 % or higher as most, if not all, of today's tablet and capsule products are – based on the applicable "process variability unknown" inspection plans in the applicable standards, ISO 3951 or ANSI Z1.9.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
VIII. A. "439-440" (Continued)	(Continued) Provided the Draft is revised to conform to the clear requirements of CGMP, instead of the commenter's suggestion, this reviewer recommends the following language for this bullet point: "• Summary of the results' data and the scientifically sound analysis ~~for~~ thereof that establishes the degree of correlation ~~of~~ between the batch-representative in-process dosage unit *uniformity results for each active* ~~stratified sampling~~ ~~with~~ and the batch-representative finished product uniformity of content results for each active ingredient." This reviewer also notes, as stated in **21 CFR 210.3(b)(12)**: "Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products," **all** testing and quality control activities are included whenever the statute or CGMP regulation uses the phrase, "manufacture, processing, packing, or holding," is used in the CGMP regulations and notes that, under "Scope," the CGMP regulations for finished pharmaceuticals (**21 CFR Part 211**) states in **21 CFR 211.1(a)**: "The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals." Hopefully, those who read this reviewer's remarks will remember what is truly the **minimum** required by CGMP and <u>not</u> what firms are currently doing or proposing.	(Continued) **21 U.S.C. 351(a)(2)(B)**: "**Sec. 351. Adulterated drugs and devices** A drug or device shall be deemed to be adulterated— (a) Poisonous, insanitary, etc., ingredients; adequate controls in manufacture (1) … (2)(A) … (B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; …" **21 CFR 210.1** (**bolding** added to the text): "**Sec. 210.1 Status of current good manufacturing practice regulations.** (a) The **regulations set forth in this part and in parts 211** through 226 of this chapter **contain the minimum current good manufacturing practice for methods to be used in**, and the facilities **or controls to be used for**, **the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety,** and **has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.** (b) The **failure to comply with any regulation set forth in this part and in parts 211** through 226 **of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated** under section 501(a)(2)(B) of the act **and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action**."
"471-475"	We recommend changing this definition to: "Stratified Sampling is the process of collecting a representative sample by selecting units deliberately from various identified locations within a lot or batch, or from various phases or periods of a process. Stratified sampling of dosage units specifically targets locations throughout the compression/filling operation that have a risk of producing failing results in the finished product uniformity of content, then random dosage units are selected within these locations. This reviewer rejects this commenter's at-best-misguided attempt to "improve" a fatally flawed definition and trusts that the Agency will do likewise.	This change would help bring this draft guidance and the PQRI definition in harmony. It also serves to clarify that this sampling strategy is a type of random sampling. By definition, it is a false assertion to claim that a sampling plan that <u>targets</u> certain "locations" in a batch to the deliberate exclusion of others is a "type of random sampling" <u>because</u> such plans do <u>not</u>, *as required to be random sampling*, take a random sample from the entire batch. Moreover, this definition ignores the clear CGMP requirement that all such samples must be a *representative sample* from the batch and, *even using the commenter's suggested revision*, the "process" proposed does <u>not</u> provide samples that are *batch representative*.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
"477"	Please consider adding "target strength" to the definitions. While this reviewer does not object to rephrasing the definition for "**Target assay** …" to read, "**Target assay or target strength** …," as the commenter's suggest, this reviewer recommends that the definition be changed to read: "~~**Target assay**~~ **Target strength** is the intended ~~strength~~ labeled or ~~intended~~ established amount of active ingredient in the dosage unit," and the draft changed to replace all instances of "target assay" with "target strength,"	Target assay and target strength are used interchangeably, but no definition is provided for target strength. Term "**Target assay**" is less appropriate since the term "**Target assay**" caries with it the connotation of an uncertain level that is "measured" whereas, in the context used, "**Target strength**" connotes, what is required, a fixed level that the process is intended to target. The definition should parallel the CGMP regulation at **21 CFR 211.101(a)**, "The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient" – any guidance definition should, where possible, be congruent with the clear applicable terminology in the CGMP regulations.
Revised Attachment 2 Top two boxes	We suggest changing STM and MTM to SCM and MCM. This reviewer does not object to the changes proposed here.	The MCM and SCM terminology need to be consistent within the guidance document. Self-consistency, accuracy, and agreement with the underlying binding regulations are all laudable features for any regulatory document.
General Comments on multilayer tablets	We suggest adding direction to industry as to how the guidance is to be applied to multilayer tablets where the actives are in different layers. The guidance should indicate how to evaluate stratified samples of bilayer tablets. Since the commenter clearly recognizes that the published Draft cannot be used to address drug products that are multiple-layer dosage units, the Agency can either restrict the guidance's Scope to "single-layer dosage units or, if it wishes to address both single- and multiple- layer dosage units adopt the approaches recommended by this reviewer in this review or those contained in the "revised DRAFT" he submitted to this docket that was posted to the FDA Public Docket 2003D-0493 on 30 January 2004. Since the CGMP regulations that apply to the in-process materials and drug products (as the title of **21 CFR 211.110**, "Sampling and testing of in-process materials and drug products," clearly states) and said regulations clearly require the assessment of the uniformity of the drug product produced at each significant manufacturing phase, it should be clear that the uniformity of each blend must be assessed for all critical variable factors. **Hopefully, the Agency will revise this guidance for the *uniformity*** (continued ➔)	If there are two different assays for the two different actives, one could be in a situation of having to apply SCM for one active and MCM for the other. First, this reviewer notes that the rationale here has nothing to do with bilayer tablets *per se* as it addresses the reality that dosage units containing more than one active that cannot be evaluated using the same test procedure may have the outcome indicated by the commenter even when said actives are present in a single-layer dosage unit. The acceptance criteria are based on weight corrected data; the guidance should also provide for use of non-weight corrected data. As this reviewer has previously established the use of weight-corrected active values to meet the in-process CGMP requirement ***minimums*** is a non-conforming choice that must not be used if you wish to comply with the clear regulations governing a firm's conduct in this regard. _____ ***of the active in in-process materials and drug products that are tablets and capsules* so that it at least conforms to CGMP regulations' clear requirements with respect to assessing the *uniformity of each active*.** This is a hope because the current draft guidance clearly does not conform.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
Attachment I Revised Attachment 1 flowchart, line 498	Please consider moving the box "Assay at least 7 dosage units per each location, weight correct each result" (from line 507) immediately after box that says "Assay 2nd and 3rd blend samples from each location. This reviewer does not support the text in the boxes or the change in placement proposed. *Scientifically sound sampling plans* and *test procedures* (inspection plans) for non-discrete materials ("blends") include sufficient multiple-aliquot assessments of sample uniformity so that the testing, within-sample, between-location and error variance components can be properly assessed without the need to perform any additional testing – hopefully, this commenter is not, *as the commenter seems to be*, advocating the use of less-than-sound inspection practices?	The dosage unit data is generally used as part of the investigation to help correlate blender problems or identify sample bias. As has been clearly established by this reviewer: 1. Sampling plans proposed for the blend sampling do not conform to the *scientifically sound* and *appropriate* requirements of either the CGMP regulations or, for that matter, inspection and analytical science 2. Active uniformity cannot be validly used to establish what is required, namely, "material uniformity for all critical variable factors including, but most certainly not limited to, the active(s) in the material being assessed. 3. The CGMP regulations clearly require the assessment of the uniformity of the characteristics, not the *biased weight-corrected characteristic* proposed here.
Attachment I Revised Attachment 1 flowchart, line 508	We recommend replacing the box that says "Assay at least 7 dosage units per each location, weight correct each result" with a box that says "Use dosage units to verify adequacy of powder mix." This reviewer rejects the commenter's proposal along with the original text because the in-process dosage units collected as the Draft suggests cannot be validly used to demonstrate the uniformity of the mix because: **a)** There is no way in the guidance provided to ensure that the dosage-unit samples are from the locations where the alleged blend sample error occurred **and** **b)** The active level is but one, *and not always the most critical one in many instances*, of the critical variable factors whose uniformity must be properly assessed in *each batch* (**USA v. Barr Laboratories, Inc., et al.**, Civil Action No. 92-1744, (**812 Federal Supplement 458 (DNJ) 1993**, "Barr Opinion") to establish the uniformity of an in-process drug-product material mix.	This addresses the situation when we have identified blend sample error so they must be used to demonstrate uniformity of mix. Factually, because there are steps between the blend sampling and the generation of the dosage units, other than weight, that contribute to the variability in the values observed in the dosage units, the level of active in the dosage units is, at best, a biased estimate of the uniformity of the active in the mix but, *because it fails to assess the levels of the other critical components in the formulation*, such cannot validly be used to verify the "adequacy of powder mix." If your manufacturing system includes sampling plans that generate "sample error" or sample bias" of the type described, then your system does not comply with CGMP and the drug products produced by such systems are adulterated and cannot, therefore, be legally offered for sale. Moreover, manufacturers have an absolute legal duty to comply with any clear regulation that the Agency may not legally contravene by publishing a nonconforming guidance (**Berkovitz v. US, Supreme Court 1988, 486 US 531, 100 L Ed 2d 531, 108 S Ct 1954**).
Attachment II Revised Attachment 2 flowchart	In the top left box, we recommend changing the first criteria to "last batch was tested using SCM and met SCM acceptance criteria" Provided the procedures and acceptance criteria are changed to be CGMP-compliant, this reviewer does not *per se* object the commenter's suggestion.	This clarification is suggested to insure that someone will not read into this that if it was tested per MCM, but met SCM acceptance criteria", then SCM is OK now.

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
Attachment II Revised Attachment 2 flowchart	In the top right box: we recommend removing the first sentence, "Last batch met STM acceptance criteria." Since **the text makes a valid "condition" statement**, the commenter's rationale is anything but clear, and the commenter's rationale does not seem to speak directly to the content of that box in the published draft, this reviewer does not support adopting the commenter's recommendation.	The first sentence does not add clarity. Simply, if the last batch was tested using MCM (or started as MCM but had to go to MCM0, then the next batch must be tested using MCM. If the last batch was tested per and met SCM, MCM would not be used. Commenter's rationale seems not to match their recommendation.
Attachment II Revised Attachment 2 flowchart	Please consider changing the box stating: "You may add results from analysis of the remaining samples" to "In addition to the stage 2 results, you may add results from analysis of remaining samples." This reviewer cannot support the commenter's suggestion because it does not match their rationale. If this commenter really intends that one should "use all previously generated data," this reviewer recommends the text be changed to simply state: "You should consider all of the valid results obtained from the testing of all samples."	The proposed change would clarify that the intent is to use all previously generated data. The use of the word "may" indicates a permissible but not necessarily suggested course of action; in guidance, the word "should" indicates an intended course of action.
Attachment II Revised Attachment 2 flowchart	We recommend adding document section numbers to a few boxes. Provided the draft guidance and the **flow diagrams** provided are revised to be fully conform to the clear applicable CGMP **minimums**, this reviewer is not opposed to adding appropriate document section identifiers to the resultant flow diagrams but would recommend that such labeling be uniformly applied.	This change would help to clarify and to connect back to the document text. If the commenter's intent is to connect the boxes in the flow diagram to the text in the guidance, then all "condition" and "decision" boxes should be labeled. This reviewer also suggests that the more appropriate term to use for "flow chart(s)" or "flowchart(s)" is "flow diagram" because the terms "flow chart' and "flowchart" are usually associated with computer programming and not with diagramming the flow of a process.
Attachment II Revised Attachment 2 flowchart	We recommend listing 3 situations that allow one to test SCM and 3 that allow MCM in a bullet list above the flow chart. Begin the flowchart with the first diamond. Use SCM routine criteria if: 1. validation was readily pass and you are just starting production, or 2. routine test for the previous batch was SCM and passed SCM criteria, or 3. routine test for the previous batch was MCM, but switching rule is met Use MCM criteria if: 1. validation was marginally pass and you are just starting production, or 2. routine test for the previous batch was MCM, or 3. routine test for the previous batch started as SCM, but had to go to MCM to pass (Continued on next page)	The suggested change would help clarify the flow because we feel that the 4 boxes at the top of the flowchart are confusing. Though the attachments provided do not adhere to them, there are well-understood rules that govern the construction of flow charts that this commenter should follow if they insist on casting these as "flowcharts." In the testing of a small number of samples from a large population, statistics-based decision rules (as these purport to be) should provide for variation in outcomes that must be ignored until a sufficient number have occurred to indicate that an action is needed. (Continued on next page)

Section/ Line(s)	Comment/Reviewer's Observation	Rationale/Reviewer's Basis
Attachment II Revised Attachment 2 flowchart	(Continued from previous page) Provided the guidance is corrected to conform with all of the clear requirement ***minimums*** of the applicable CGMP regulations, the sample number minimums are corrected to "50 batch-representative dosage units" for "SCM" and "200 batch-representative dosage units" for "MCM," and the statistically flawed switching rule for switching from "SCM" to "MCM" based on a single excursion are corrected, this reviewer does not object to the modified form of a "flow diagram." However, if the commenter insists on making these "flowcharts," the commenter should revise this suggestion to conform to the well-understood rules governing flowcharting. Finally, based on this reviewer's observation and basis statements, this reviewer would recommend the following text for the commenter's suggested text: "Use 'MCM' criteria as your basis Inspection Plan when: 1. The initial process conformance batches have established that a "normal" inspection plan should be used. 2. You are just starting production and have not yet produced more than 10 consecutive batches that met the MCM criteria. 3. You do not produce more than 15 batches in any run or campaign. 4. Routine testing for the previous batch was MCM, or 5. Routine test for the previous batch was started under "reduced" inspection ("SCM"), but had to be inspected under a "normal" inspection plan ("MCM") or an augmented inspection plan (not provided in this guidance" and this is the third such occurrence in the last 5 consecutive acceptable batches. 6. The previous batch was rejected. 7. The previous five (5) batches were inspected under an "augmented" sampling plan (not provided) and met the "MCM" criteria Use "SCM" criteria your basis Inspection Plan when: 1. The initial process conformance batches have established that, under certain conditions, a "reduced" inspection plan can be used. 2. Production is at a steady rate. 3. Your initial, post-conformance studies have produced more than 10 consecutive batches that met the MCM criteria and you are authorized to switch to an "SCM" plan. 4. The routine test for the previous batch was "SCM" and passed "SCM" criteria. 5. Your current campaign consists of at least 10 consecutive batches and the routine test for the previous 5 batches was "MCM," but each batch met the "SCM" criteria.	(Continued from previous page) This draft and this commenter seem to have recognized this when they require NLT 5 consecutive batches that are tested using a "full" set but pass the "reduced" set criteria before switching from "MCM" to "SCM." However, the proposed rule for "SCM" to "MCM" has no such similar valid provision. Furthermore, before a "reduced" inspection plan (the "SCM" plan here) can validly be considered for implementation, the valid use of any "switching rules" in inspection requires (based on the controlling guidance provided in applicable recognized consensus standards, ANSI Z1.9 (and ISO 3951): 1. Production to be at a steady rate, and 2. Initially, at least 10 batches have been inspected using the normal inspection plan (the "MCM" plan here) without any being rejected. Thus, unless the production process: a) continually produces batches without interruption, or, when production is intermittent, b) produces more than ten (10) batches in each campaign the use of any reduced ("SCM") inspection is, at best, difficult to justify. Yet, this reviewer notes that this guidance failed to mention much less address the preceding realities. Finally, for those who claim that testing "200" is onerous in batches upwards of 250,000 in size should note that the number in question is less than 0.1 %! (1 in a 1000) of the units in the batch for such batches and less than 0.01 % (1 in 10,000) for batches larger than 2,000,000 dosage unit (a "batch size" that is becoming increasingly common today – a size that should soon trigger a revision to the recognized consensus standards because their current tables end with sizes of 150,001 to 500,000 and 500,001 and over, the table needs at least one (1) additional level (probably at 2,000,000 as follows: Replace: "500,001 and over" with: "500,001 to 2, 000,000," and Add: "2,000,001 and over."

Hopefully, this reviewer's remarks have adequately addressed the numerous formal comments submitted by this commenter.

C-08 Comments By Johnson &Johnson Pharmaceutical Research & Development, LLC, Posted 11 March 2004

The Johnson & Johnson comments begins by stating:

"The above referenced FDA draft guidance entitled Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment, issued October 2003 has been reviewed by scientists at Johnson & Johnson Pharmaceutical Research and Development, LLC and Johnson & Johnson affiliates. The following comments represent the general impressions of our scientists concerning issues of great importance to our business."

Johnson & Johnson's reviewed comments are as follows:

"General Discussion:

Scientists from various functional groups within our organization closely reviewed and discussed the implications of the draft guidance proposals to development products, newly approved products and established marketed products. Despite much debate, the group recognizes FDA's motivation to create a consistent approach regarding the GMP requirements for blend uniformity testing. Further, our scientists recognize the guidance recommendations as a furtherance of FDA's science-based manufacturing and PAT initiative. The group has no objection to the proposed recommendations for drug products in development and newly approved drugs and believes it will bring positive outcomes for both pharmaceutical manufacturers and customers."

First, this reviewer is heartened by the commenter's admission that there are "requirements for blend uniformity testing" even though the commenter incorrectly portrays them as "GMP requirements" instead of the CGMP (current good manufacturing practice) regulations that they most clearly are.

Moreover, this commenter miscasts the etiology of the Draft as "a furtherance of FDA's science-based manufacturing and PAT initiative."

Historically, the current draft has it origins in the aftermath of the 1993 "*Barr*" case where the presiding official, Judge Wolin, wrote an opinion (**USA v. Barr Laboratories, Inc., et al.**, Civil Action No. 92-1744, (**812 Federal Supplement 458 (DNJ) 1993**, "Barr Opinion") in which, *based on the information presented at trial and his reading of the applicable CGMP regulations*, he correctly concluded that (final) blend testing was required for *each batch* of drug product ("In the *Barr* opinion (¶ 64), one of Judge Wolin's findings was blend testing is required for 'and ordinary production batches.'").

Moreover, **21 CFR 211 Subpart F—Production and Process Controls** clearly supports the "each batch" requirement that Judge Wolin recognized.

The last important milestones before the Agency issued this Draft are the Agency's issuance in 1999 of a draft guidance entitled "Guidance for Industry ANDAs: Blend Uniformity Analysis" which, because of industry objections, the FDA formally withdrew on Friday, 17 May 2002.

Thus, the present draft guidance is a "furtherance" of the Agency's more than decade long attempt to provide *CGMP-conforming* (as required by law) guidance on blend uniformity that articulates at least one *scientifically sound* and *appropriate* approach to ensuring compliance with the requirement ***minimums*** set forth in the applicable CGMP regulations.

Moreover, this attempt is not truly the Agency's; it is rather an Agency draft guidance based on a "recommendation" document from the PQRI, an industry front organization that, *based on the lack of sound science or references to the applicable recognized consensus standards published by ISO and ANSI*, crafted its "recommendation" to fit current industry practices with little or no regard for what is legally required or scientifically appropriate.

Thus, this reviewer is not surprised that this commenter has "no objection to the proposed recommendations for drug products in development and newly approved drugs and believes it will bring positive outcomes for both pharmaceutical manufacturers and customers."

"Our scientists are primarily concerned about the implications of the draft guidance recommendations to established marketed products and request that the draft guidance clearly state whether or not the draft guidance applies to marketed products."

Since, as Judge Wolin opined and this reviewer knows, the CGMP regulations apply to each batch of drug product and the Agency is charged by law [J&J1] with issuing documents that conform to the clear requirements set forth in any binding regulation, this reviewer knows that the FDA should clearly state that, *whatever the final CGMP-conforming guidance the Agency issues on "Blend Uniformity Analysis," "Powder Blends and Finished Dosage Units – …," or other suitable CGMP-conforming title*, the final guidance applies to all drug products, developmental, new or old – since, by law, all drug product batches must meet all of the applicable clear requirement ***minimums*** of the CGMP regulations for drugs, including the applicable clear ***minimums*** set forth in **21 CFR 211 Subpart F** that require each batch to be assessed at each significant phase during manufacturing for the uniformity of all critical variable factors, including, but not limited to, the uniformity of the level of the active or actives in each in-process material and in-process drug product that contains such.

[J&J1] In the 1988 United States Supreme Court decision, Berkovitz v. USA [**Berkovitz v. US, Supreme Court 1988, 486 US 531, 100 L Ed 2d 531, 108 S Ct 1954**], the Court *unanimously* held that it is not legal for an FDA administrator to publish any document that is at odds with a clear binding FDA regulation.

"We believe that the stratified sampling and powder blend uniformity testing recommendations should not apply to established marketed products. Application of these additional requirements would impose an unreasonable burden (sample handling and shifting batch-testing criteria logistics) upon proprietary pharmaceutical manufacturers for established marketed products where out-of specification results are few and considerable historic data already exist."

By law, the blend uniformity testing of each batch is, and has been since the late 1970's a clear CGMP regulation requirement ***minimum***.

As this commenter knows, guidance does not and cannot impose any "additional requirements" – guidance simply provides recommended courses of action that, by law, are supposed to be CGMP-conforming and, hopefully, are.

Thus, as long as this commenter complies with the clear requirement ***minimums*** of the CGMP regulations as they apply to in-process materials and in-process drug product, the commenter is free to comply with said regulations in the manner they elect.

However, as the commenter knows, this commenter is not free *not to comply* with any clear CGMP regulation.

Thus, this reviewer is at a loss to understand the commenter's repeated specious "additional requirements" rant.

As to the commenter's statement concerning "established marketed products where out-of specification results are few and considerable historic data already exist," this reviewer offers the following observations:

1. If you don't test *representative samples* from *each batch* in the manner required by law (and, in general, the industry does not seem to do this), then you have no valid "historic (sic)[J&J 2] data."
2. Ask those injured and the families of those killed by the most recent case, the "undetected" out-of-specification inhalers, what they think of the industry's current apparently non-compliant practices.
3. Ask yourself, are you certain that each batch of each drug product manufactured by the industry comes close to the CGMP expectation that **all** released dosage units (the ones you didn't test) should, if tested, meet the **USP**'s post-release, in-commerce requirements? —
   - ❖ If your answer is "YES," then, what is the reason for the ongoing recalls of released drug product batches for uniformity-related failures?
   - ❖ If your answer is "yes" or, every statistician's "probably," then, why, as the draft guidance, does the PQRI's recommendation document falsely equate "active uniformity" to "batch uniformity" (or do you really believe that the uniformity of the other components in the formulation is of no consequence) and why, as this draft, does the PQRI only address "active uniformity" when many of the recalls are "dissolution" failures that implicitly implicate the uniformity of the components in the formulation that affect/effect/control the availability of the active to the patient?
   - ❖ If your answer is "probably not," "no," or "NO," then, why does your firm release such batches?

J&J 2 The proper word is "historical", *meaning* providing evidence for a fact in history, not "historic," *meaning* famous in history.

"Rather than impose new requirements for all drug products, we believe a compromise approach should be adopted. Under this approach, the requirement for stratified sampling and powder blend uniformity testing would apply to development and newly approved drug products but not to established marketed products it the integrity of the manufacturing process and drug product can be demonstrated historic data. We believe this approach supports FDA's goal to establish a consistent approach to GMP blend uniformity and the furtherance of science-based manufacturing and PAT initiative."

Because, as this commenter knows, guidance does not and cannot impose any "additional requirements, " this draft guidance cannot and does not "impose new requirements for all drug products" – again, all guidance simply provides recommended courses of action that, by law, are supposed to be CGMP-conforming and, hopefully, do conform.

Based on this reality, the Agency should reject the commenter's proposal.

Further, this reviewer notes that the applicable CGMP regulations clearly require a *representative sample* (**21 CFR 211.160(b)(2)**) for in-process materials and in-process drug products, which, in turn, requires "representative sampling" (sampling in a manner that ensures that each sample is a *representative sample* (as the term *representative sample* is defined [**21 CFR 210.3(b)(21)**]).

Since, *as defined in the draft or amended by other commenters*, the Draft's *stratified sampling* does not, as defined, take a *sample* that is *representative* of all portions of the material (blend or dosage unit) that is being sampled, this reviewer suggests that this terminology be removed from the draft guidance as it clearly does not conform to the clear definitions and requirements set forth in the CGMP regulations.

Finally, as all true scientists know, unless a body of "historic (sic) data" contains data that is truly "*batch representative*" of each critical variable factor (e.g., for "final blends," active(s), release control agent(s) [including disintegrant(s) and active-release mitigating agent(s)], lubricant(s), stabilizer(s), water, residual solvents, impurities; for "formed dosage units," active(s), availability of active(s), stabilizer(s), water, residual solvents, impurities, content weight), a body of non-batch-representative data from each batch manufactured, *as the commenter seems to be proffering here*, cannot validly be used to demonstrate the true "integrity of the manufacturing process."

Properly, such *historical data* should only be used to verify:

c) Acceptance percentage for the batches that were started,
d) Apparent variability of the results obtained for the samples tested, **and**
e) Category for the batches (based on the percentage of batches that fall within each of the possible testing regimes for each critical variable factor in the drug product).

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

C-09 Comments By Amgen, Posted 11 December2004

The Amgen comments begins by stating:

"Amgen Inc, is pleased to provide these comments on the Draft Guidance for Industry on Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment. Amgen Inc. is a global biotechnology and pharmaceutical products company based in Thousand Oaks, CA."

Amgen's reviewed comments are as follows:

"**Comments:**

Point #1
Predict In-Process Dosage Form Uniformity When RSD of Blend Sample is Smaller Than 3%

In accordance with PQRI data mining, blend uniformity (BU) data is predictive of final dosage form uniformity when blend RSD is less than 3% (Ref 1). Content Uniformity (CU) is highly correlated with Blend Uniformity. Therefore, if data development showed consistent BU with RSD less than 3 %, the proposed stratified sampling plan for exhibit and/or process validation batches (e.g., 3 replicate samples per location from 20 locations) could be reduced to fewer samples/locations.

(Ref) 1. Product Quality Research Institute /Blend Uniformity Working Group (PQRI/BUWG). Data mining. Results of PQRI Datamining Effort, Report slides prepared by Tom Garcia (Chair, PQRI/BUWG). December 12, 2001.
http://www.fda.gov/ohrms/dockets/ac/01/slides/3804s1_06_garcia-boehm/sld048.htm
http://www.fda.gov/ohrms/dockets/ac/01/slides/3804s1_06_garcia-boehm/sld045.htm"

Though this reviewer does not have access to the underlying data and the assumptions made, this reviewer is certain that the commenter's viewpoint is flawed because it discusses "sample" RSD, or, more properly the "sample estimate of the RSD" for an active, when what is required is to ***predict*** *batch uniformity* for ***all*** *critical factors* (based on the batch's mean, variability, and distribution of values for all such) not just the batch's active uniformity.

In addition, if, *as the commenter asserts*, the "observed" critical RSD for the active level is 3 (or less) before the sample estimates of the uniformity of the active in the blend are "predictive" (in a 2001 presentation by an undefined PQRI data mining technique at an unspecified confidence level) of the uniformity of the active in the final dosage form, then why didn't the PQRI recommend "3% RSD" as the cutoff for "readily passing"? Or why isn't this commenter recommending that in the comments to the docket?

Instead, this commenter continues to treat *sample* statistics as if they were somehow *batch* statistics when nothing could be further from the truth.

Unaware of this difference or its importance, or indifferent to it, this commenter focuses on reducing the number of samples and locations.

Hopefully, the Agency will, however, take the information this commenter has provided to heart and revisit the issue of what should be upper limit for the sample estimate of the RSD which now appears to be for active uniformity at least closer to "3%" than the "4%" or "6%" numbers that the PQRI furnished to the FDA a year later in its December 2002 "recommendation."

Moreover, this reviewer's examination of the plots of results from actual batches was very informative in that it confirmed that the sample numbers (though not shown) for the various batches were less than *batch representative*, the plots commingled direct compression (12), wet granulation (67) and dry granulation (70) data, and seemingly plotted the observed sample estimates of the RSDs for the dosage forms against the corresponding blend RSDs because the slides did not indicate that the presenters had, as they should have "corrected" the RSDs (to correct for the differences in the numbers of samples tested to compute the RSDs reported to the maximum RSDs for that number of samples or, failing that, separated the data into sets where the same numbers of samples were tested.

This reviewer found another "nuggets of gold" in the Reference 1's Slide 42,

"• Conclusion: Computer simulations to estimate criteria rejection rates yield slightly smaller values (conservative) than the reject rates based on actual data."

This reviewer found that slides "**(conservative)**" remark especially interesting because it equated the simulations underestimating the actual situation as "conservative" rather than, *had the author's concerns been safety and quality oriented*, problematic.

Hopefully, those who read this reviewer's comments will get it – **the *critical issue* is** not whether the sample passes, but ***whether the sample results are sufficient to predict*, with some high degree of confidence, *that the batch of untested materials will***, if the subsequent process steps do not fail, ***produce a batch of acceptable drug product.***

"**Point #2**
Choice of Sampling Plans When Total RSD Is Smaller Than 3%

In accordance with the Final PQRI Blend Uniformity Working Group Recommendation (Figure 2, Between Location Variability Exists- Ref 2), the"20x3, 7" sampling plan and USP content uniformity test method for tablets are compared for increasing total variability (between location RSD varies from 1-10%, while maintaining the % RSD values for both weight variation and assay each at 1.5%). As the total RSD is smaller than 3%, the two sampling plans give the same close to 100% probability of meeting acceptable criteria. Therefore, if the BU and CU RSDs are less than 3% in demonstration batches, it should be sufficient to only test the CU of the final product without testing blend or stratified samples in routine manufacturing.

(Ref) 2 Product Quality Research Institute /Blend Uniformity Working Group (PQRI/BUWG). December 31, 2002. Final Blend Uniformity Recommendation: *The Use of Stratified Sampling or Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends*. http:/www.pqri.org/dataminimg/imagespdfs/011003rec.pdf"

The commenter's remarks here have made it crystal clear to this reviewer that this commenter not only does not understand the clear legally binding requirements of the applicable CGMP regulations governing in-process materials and in-process drug products (which *clearly* require the testing of each in-process material and drug product during manufacturing and the control of the release of in-process materials and in-process drug products at the beginning or completion of each significant product manufacturing phase), and/or is oblivious (knowingly or otherwise) of any of the consequences of willful non-compliance therewith.

Factually, you cannot know the degree of agreement between the active uniformity of next blend and the dosage units produced therefrom unless you evaluate the active uniformity in the product produced by each stage.

Past success is no guarantee of future process performance *especially when the critical properties of all components are not adequately controlled*.]

Since most firms lack rigorous controls on all of the critical physical and chemical properties of the components they use to manufacture their drug products and, in many cases, have no controls or meaningless controls on the key physical properties of their components even though these are known to affect the ability to attain and maintain a uniform stable blend, each campaign (and, in some cases, each batch) is a new adventure whose probable outcomes cannot be validly predicted from the body of historical data on that drug product or, *for that matter*, from the performance observed during the last campaign or, in many instances, for the previous batch.

Finally, in a multiple-step process that manufactures products from components, one of the key quality precepts in controlling overall cost is that one should design your control systems so that they detect non-conforming components, materials, and intermediate products as early as possible in the production as you can.

This commenter's remarks here clearly indicate that minimizing such costs is not a priority to this commenter.

Apparently, this commenter is certain that the recent monetary and consent decree costs incurred by Schering-Plough, a company that apparently shared this commenter's view on not complying with the in-process CGMP requirement ***minimums*** for the inspection of a *batch-representative sample* of the output of each stage for *each batch* of drug product, cannot happen to them.

Moreover, the commenter's focus on the *sample* results from *samples* (which may not be *batch representative* and, if the draft guidance were followed, most certainly would not be) clearly indicates that this commenter does not truly care if the untested released batch (the 99.9+ % of the units), from which the samples tested (the < 0.1 % to < 0.01 % were withdrawn, does or does not meet its post-release **USP** requirements – all they want is for the few samples tested to pass – whatever that means.

"**Point3**
Apply the Guidance to Approved Products

There is a lack of guideline on how extensive the Stratified In-Process Dosage Unit Sampling as specified in this Guidance should be applied to already approved products. For example, existing data from demonstration batches should be used to determine what criteria of routine testing to use without generating new data."

This reviewer finds the commenter's statements here to be problematic.

If the commenter's firm is complying with all the CGMP minimums for each stage or phase in the manufacture of each batch of drug product that are applicable to their drug products as said firm should be, then the commenter should probably ignore this Draft and, *even when a CGMP-conforming guidance on this topic is finalized*, the FDA's final guidance on this topic.

This is the case because the commenter's firm will already be appropriately inspecting (in a fully CGMP-compliant manner) not only each final blend and in-process drug product but also the components and materials produced prior to the final blend using sampling plans that take and test unbiased *batch-representative samples* and analyze a *batch-representative* set of unit-dose aliquots or units from each sample sampled for all of said samples' critical variable factors, not just the active content – and, *since their controls are fully CGMP compliant*, the firm need not be concerned with the details in the FDA's guidance.

If, on the other hand, the commenter's in-process controls for the final blend and the formed dosage units are not fully compliant, *as the commenter's statements here seem to indicate*, and/or the firm does not fully inspect *batch-representative samples* from *each batch at each significant phase during manufacturing and/or include controls appropriate to the batch for the appropriate critical variable factors*, the firm should phase out, as rapidly as possible, manufacturing and releasing such adulterated products into commerce.

Moreover, *until the FDA publishes CGMP-conforming guidance that truly addresses all aspects of this topic*, such firms should develop, implement, file (CBE-0) their improved controls (specifications, standards, sampling plans, test procedures and other controls) and the data that supports them, and, *when the FDA acknowledges receipt of their submissions*, phase in the fully CGMP-compliant manufacturing of their approved drug products.

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

C-10 Comments By Wyeth Pharmaceuticals, Posted 11 March 2003

The Wyeth comments begins by stating:

"Wyeth Pharmaceuticals is submitting the attached comments (attachment 1) on the FDA's draft guidance dated October 2003 on ***Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment.***

Wyeth is one of the largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer and marketer of prescription drugs, biologicals and over the counter medications. As such, Wyeth supports the comments submitted by the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Parenteral Drug Association (PDA). We have highlighted a number of points discussed with the representatives of these organizations that we believe are of particular importance (attachment 2)."

Wyeth's reviewed comments contained in the tables provided in Wyeth's "**Attachment 1**" for containing Wyeth comments and "**Attachment 2**" containing comments discussed with the PDA and PhRMA can be found in the tables that begin on the next page.

To facilitate the reading of these comments, this reviewer has combined the commenter's' "***Section***" and "**Guidance Line**" columns into a single "***Section G-Line***" column.

In general this reviewer's "**Observation**" follows the Wyeth "**Comment**" and his "**Basis**" statements follows the Wyeth "**Rationale**."

"Attachment 1
Wyeth Comments: FDA Guidance …"

Section **G-Line**	**Comment / Observation**	**Rationale / Basis**
III. 60-65	Remove definition from Scope Though the text in question is more than a definition, this reviewer does not object to moving/removing this text provided such placement will ***truly*** improve the "**Scope**" statement.	This is a definition and should not be in the introductory paragraph of the Scope. Only Lines 60-62 are a definition. The other sentences in Lines 62- 65 discuss the "test results" obtained from "locations in the compression /filling operation that have the greatest potential to yield extreme highs and lows in test results."
III. 67-72	Move to Introduction This reviewer does not object to the move indicated.	Provides clarity and strengthens the flow of the document by moving this section to the Introduction.
III. 74-86	For clarity, move to line 60 and suggest rewording as follows: Line 74 (new 60): " This guidance suggests procedures to ensure adequate mixing and dosage uniformity via following steps:" This reviewer: **a)** supports the repositioning of the text as the commenter propose, **b)** objects to the misleading language revision, and **c)** proposes the following alternative: "This guidance suggests procedures to ~~ensure~~ **address the** adequate mixing **of the active or actives in the final blend** and the dosage uniformity **for the active or actives in the formed dosage units** via following steps:" Also suggest adding the following bullet as the first bullet. "Conduct sample blend testing procedures by evaluating appropriate sampling thief design, appropriate sample size and sampling technique" Though this reviewer does not object to the proposed bullet *per se*, he does not agree with the commenter's text and proposes the following alternate text: "*Use sound inspection science to* establish valid inspection (sampling and testing) procedures that: A. *For the blend*, take minimally invasive samples of sufficient amount to provide for the unbiased subsampling of at least three times the number of duplicate unit-dose aliquots that would be required for the evaluation of all of the critical variable factors in the blend, including the active or actives, as well as at least one unbiased aliquot of sufficient size for each assessment of the key bulk physical properties of the blend, including its bulk and tapped density. (Continued on next page)	Better define the purpose of the Guidance Document. While this reviewer lauds the commenter's statement, he notes that the commenter's suggestion fails to do as the commenter suggests it will. Since the text in this draft guidance clearly only addresses the measurement of the active or actives in the final blend and the dosage units, the statements made should match what the guidance provided factually addresses. Moreover, the procedures suggested can only be used to address not ensure – only the outcomes observed can be used to ensure. Currently, the published draft guidance does not address testing procedures for evaluating thief design, sample size, and sampling techniques, and it should not – such should be left up to the manufacturer. What is really needed is a bullet to suggest that sound inspection science should be used and to, in general, outline the approaches to batch-representative sampling that the firms should use for the different types of samples (non-discrete and discrete) and sources of samples (dynamic and static). These approaches should provide for the sampling of more (in amount or number) than the most intensive testing plan requires for all of the critical variable factors, including the active or actives, in order to ensure that no "resampling" is required because, in the static case, it is difficult to sample from the exact same location and, for dynamic sampling, it is simply not possible. (Continued on next page)

Section **G-Line**	**Comment / Observation**	**Rationale / Basis**
III. 74-86 (Continued)	(Continued) B. *For the dosage units*: 1. *When static sampling is used*, ***randomly*** select (from across and throughout the batch) not less than four (4) times the number of *batch-representative* samples required for all testing of any critical variable factor for which the test is adversely impacts the integrity of the dosage-units tested as well as at least two (2) times the number of batch-representative samples required for any *critical variable factor* for which the test does not impact dosage-unit integrity. 2. *When dynamic sampling is used*, establish a sampling plan that samples at sufficient points across the dosage-forming step to capture the variability of the blend as it impacts the active content in the dosage units formed and, at each sampling point, collect an appropriate multiple of the dosage forming stations to capture the local variability at each sampling point in a separate container for each appropriately identified sampling point. [**Note:** The total number sampled should be not less than the number required for the *static sampling* case.]	(Continued) [**Note:** In the case of dosage units, this reviewer notes that many firms use double sampling "ANSI Z1.4" ("MilSpec 105E") type inspection plans that, for production-scale batches, take 1600 to 2500 samples, these firms should not mind using their "Z1.4" samples that should have been taken as outlined and, *after they pass their non-destructive "Z1.4" visual inspection criteria*, using them for their "Z1.9" testing requirements provided, *for dynamic sampling*, the sample from each sampling point has been collected in a separate container tied to the sampling point at which it was taken. Thus, such firms should not object to the number of dosage-unit samples sampled as being onerous because they already take that order of magnitude of samples. Obviously, their complaints about the number of samples is really a complaint about the number that are required to be tested, *at a confidence level of 95 % or higher*, for the results obtained to presumed to be *batch-representative*. Perhaps if these firms spent more time developing tests appropriate for assessing uniformity that do not require a separation step rather than complaining about the costs in money and time their separation-based methods would require, they would find that such methods are not only "10 times" faster but also furnish results that are 2 to 3 times less influenced by the measurement system than their current methods.]
III. 99-101.	For clarity, suggest the lines to be reworded as follows: "When using the methods described in this guidance, certain data may reflect trends. We recommend that manufacturers scientifically evaluate how these trends may affect the quality of a product. " This reviewer does not and cannot support the commenter's proposed rewording and, *if any change is needed in this paragraph*, proposes the following for this *obviously misplaced paragraph* (that does not belong in a "**SCOPE**" section): "When using the ~~methods~~ **procedures** described in this guidance, certain **unexpected** data or **adverse** trends may be observed. We recommend that manufacturers scientifically evaluate ~~these types of research data to~~ such **findings and** determine ~~if~~ **the extent, if any, to which** they **adversely** affect the quality of ~~a~~ **the batch or batches with which they are associated and the integrity of the process used to manufacture the** product. The FDA does not intend to inspect "research" data collected on an existing product for the purpose of evaluating the suitability of **any of the** proposed methods **unless it is a part of an investigation into a proven failure of the batch, whether released or not, to clearly meet any of its sample specifications and batch acceptance criteria**. Any FDA decision to inspect **any other** research data would be based on exceptional situations similar to those outlined in Compliance Policy Guide Sec. 130.300.[8] Those data used to support ~~validation~~ **initial full-scale process qualification studies** or regulatory submissions will be subject to inspection in the usual manner."	Provides clarity. Contrary to the commenter's stated rationale, the rewordings proposed change the meaning of the text. Second, though ignored by this commenter, this paragraph is out of place; it does not belong in a "**SCOPE**" section. Moreover, this "out of place" paragraph seems to have been lifted from the Draft "PAT" guidance and inserted in the scope of a Draft guidance that purports and is represented to address CGMP-compliance issues. Factually, if the results clearly indicate a batch failure that requires an investigation (and all such failures do require an investigation), the paragraph is at odds with the CGMP regulations for drug products (**21 CFR 211.192**, "… Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. …") not to mention the Agency's policy of reviewing all investigations. [**Note:** Under CGMP, **all** batches are "validation" batches.]

Section **G-Line**	**Comment / Observation**	**Rationale / Basis**
IV. 113	Change the word "how" to "procedures". This reviewer agrees with the change proposed by the commenter here.	Provides clarity.
IV. 125-139	Create sub0bullets to distinguish between the different steps. For example: • Develop blend sampling techniques. o Extensively sample the mix in the blender and/or intermediate bulk containers (IBC). o Identify separate blending time and speed ranges, dead spots on blenders, and locations of segregation in IBCs. Determine Sampling errors. o Define the effects of sample size (e.g., 1-10X dosage unit range) while developing a technique capable of measuring the true uniformity of the blend. Sample quantities larger than 3X can be used with adequate scientific justification. Appropriate blend sampling techniques and procedures should be developed for each product with consideration to the various designs of blend powder sampling and the physical and chemical properties of the blend components. • Design blend-sampling plans and evaluate them using appropriate statistical analysis. • Quantitatively measure any variability that is present among the samples. Attribute the sample variability to either lack of uniformity of the blend or sampling error. Significant within-location variance in the blend data can be an indication of one factor or a combination of factors such as inadequacy of blend mix, sampling error[9] or agglomeration[10, 11]. Significant between-location variance in the blend data can indicate that the blending operation is inadequate. While no opposed to sub-bullets, this reviewer finds that the commenter's suggested changes are, in general, wrongheaded because the focus is on studying the problem (final blend non-homogeneity and instability) rather than, as it should be, solving the problem (generating stable homogeneous final blends). In addition, it does <u>not</u> clearly address the separate issues of appropriate amount to sample from the amount to test. Taking their comments and the preceding into account, this reviewer offers the following alternative (that starts in the adjacent column ➔ and finishes in this column on the next page)	Provide clarity. We propose a hierarchy for the first three bullet points because their relationship to each other and the fact that they separate development from the blend sampling execution. ——————————————— • **Develop general controls on** o component specifications, and o blender loading, unloading, and blending regimens that eliminate 'dead spots' in the blender and 'segregation' on storage in the IBCs. • ***Using the general controls developed,* interactively develop:** o Blends that are uniform and mechanically stable. o Blend-sampling procedures that are: – Minimally invasive, – Take *batch-representative* samples, and – Ensure that each sample sampled is: – Minimally biased and – Sufficient to provide an amount that is at least 3 times the amount needed for duplicate unit-dose evaluations of each sample for all critical variable factors that must be independently evaluated as well as 2 times the amount for any bulk physical-property assessment. o Blend-aliquot-sub-sampling procedures that are: – Minimally invasive, – Minimally biased, – Reliably sub-sample unit-dose (or smaller) aliquots for testing from each sample sampled to ensure samples tested are batch representative, and – Take duplicate unit-dose (or smaller) aliquots for not less than 30 % of the samples sampled to ensure that the test results will contain sufficient sample-location data pairs for the valid estimation on "within-sample variance" – Evaluate each aliquot prepared in a manner that either averages multiple measurements to minimize the measurement contribution to result variability or, *when that is <u>not</u> possible*, make at least duplicate measurements on each aliquot and use the average of the two as the result value and the range estimate of the standard deviation from which your measurement variance estimates should be computed. (Continued on next page)

Section **G-Line**	**Comment / Observation**	**Rationale / Basis**
IV. 125-139	(Continued) • ***When a uniform mechanically sable blend has been developed***, **conduct blend analysis** on batches by extensively sampling the mix in the blender and/or intermediate bulk containers (IBCs) using the blend-sampling and "unit dose"-blend-evaluation procedures you have developed • ***Provided all of the observed average values for the multiple measurements made on each aliquot tested are within the scientifically sound and appropriate predetermined limits specified, at the 95-% confidence level or higher***, **estimate the following parameters:** a. batch mean (must be within the range from " – 0 %" to "+1 % or less" of the target for actives), b. batch variance (should be, based on PQRI's real data, less than 3 % for actives), c. batch range (should be not greater than the range from > 85 % to < 115 % of the batch mean observed for the actives) d. testing variance, e. within-location variance, f. between-location variance, g. sampling variance, and h. "random" error variance component **for each variable factor, including each active level, evaluated**. • **Use these values to estimate** the true batch mean and limit values and the minimum "process" manufacturing capability for each of the critical variable factors in the blend as well as the overall manufacturing capability for each batch's blend. • ***When there is significant residual between-location variance in the blend data***, **the manufacturer needs to ascertain what combination of improved controls** (on the physical properties of the components, formulation, blender loading, blending regimen, and, where the blender is unloaded into IBCs, blender unloading, IBC storage and IBC sampling) **are needed to render the blend both uniform and physically stable**. (***First bullet***.) • ***When sufficient reproducibility in findings has been achieved on at least two (2) blends***, **review the full set of sampling locations used to characterize each blend and**, provided all of the results are comparable and meet all specifications, **select the minimum set of batch-sampling locations that is *representative* of the *batch*** as the set you will use for "normal" or "routine" blend sampling. • **Finalize, review, audit, approve, and convey all data and findings in the appropriate quality-unit approved report**.	(Continued) Hopefully, the more logical, comprehensive, and CGMP-compliant approach presented will help both the industry and the Agency understand at least one inspection science based approach to the development of a rugged uniform blend and the sampling and testing of said developed blends.

Section G-Line	Comment / Observation	Rationale / Basis
IV.B. 158	The purpose of this statement is not clear. We suggest that it be deleted unless it can be clarified. This reviewer agrees with the commenter's suggestion to delete this bullet point.	The use of this definition is not consistent with the definition provided in the document's glossary. This statement is unclear. This commenter strikes this bullet point, as it is not pertinent to the case at hand where the dosage-unit data are to be compared with the previous final blend data for the same batch. This is the case because, *given the lack of rigorous controls on the physical properties of the components used*, the blend results from one batch cannot be validly compared to the dosage-unit results from some other batch.
IV.B. 161 and IV.C. 183	This section refers to development batches only and may not be the actual process that will be validated. Providing summaries from early stages (not commercial scale) of development may not be fully representative. Only data supporting validation should be required. This reviewer cannot agree with the commenter's characterization of reality and does not do so. The lifelong journey of a product developed under a full validation journey consists of six general qualifications (Qs) (initial Design/Development Q, initial Build Q [a/k/a IQ], initial Operation Q, initial Evaluation Q [a/k/a PQ], ongoing Maintenance Q, and final Closure Q). For a legacy system/product, the first four Qs can be replaced by four corresponding verifications (Vs) activities (initial Design/Development V, initial Build I [a/k/a IV], initial Operation V, and initial Evaluation V [a/k/a PV].	**Note:** The commenter furnished no rationale for their remarks. If for no other reason, the development data should be included because it shows the historical steps by which the full-scale manufacturing system was developed as well as provides the basis data from which the specifications, standards, sampling plans, testing procedures and other controls were established. In addition, the commenter's remarks are at odds with the reality that validation begins in the development phase as **21 CFR Part 820**, for medical devices, more clearly enunciates.
IV.B. 168-170	Recommend a specific reference to PAT, for example by adding "such as PAT" to the end of the sentence on line 170. While this reviewer understands the commenter's intent, as other commenters have, the current guidance is not applicable to systems that do not analyze but rather classify materials, as the systems touted under PAT seem to do. Thus, this reviewer cannot support the commenter's suggestion here until he sees scientifically sound evidence that such classifications systems can be properly trained to classify physically unstable mixtures of multiple-component solids having wide-ranging physical and chemical property characteristics (e.g., pre-blends, granulations, and final blends produced in the manufacture of drug products).	Provides clarity of what " alternate state-of –the art methods" means. The sentence implies that PAT could be used. Apparently this commenter does not understand that PAT, as it is being touted, relies on material evaluations systems that classify rather than analyze (or test – the usual connotation of analyze) materials. [**Note:** In complex solid-mixture materials such as final blends, the most often touted PAT systems (NIR systems) are limited by their short probe's penetration depth (ca. 3 mm) and the magnitude of the valid training set that would have to be used to cover not only the variability in the active but in its shape, morphology, particle size distribution, surface area, and the corresponding levels for all of the components in the formulation. Conservatively, for a 5-component formulation a training set would need to consist of all possible combinations of at 4 appropriate levels of each component from lots of components that span the spectrum of physical properties of each component (or, in simple terms, hundreds of carefully prepared mixtures whose physical stability would somehow have to remain unchanged so that repeat evaluations could be made).]

Section **G-Line**	**Comment / Observation**	**Rationale / Basis**
V & VI General Comment	Suggest combining Section V and VI under the proposed heading of " V. Evaluation of Exhibit/Validation Batch Powder Mix Homogeneity". This reviewer suggests that the Agency reject the commenter's baseless suggestion. If the criterion for combining sections is that certain terms are mentioned in them, then, the entire guidance should have no sections.	Both sections refer to Exhibit/Validation batches. The commenter's justification is non-persuasive because other sections refer to "validation" batches. Moreover, these sections speak to different issues. Section "**V.**" speaks to active uniformity studies in demonstration and initial conformance batches. Section "**VI.**" speaks to active uniformity and the evaluation of the results from the studies in Section "**V.**" and, *where needed*, other studies required to establish *scientifically sound* specifications, standards, sampling plans and test procedures that are appropriate for each of the materials being evaluated (final blend and dosage unit) in "routine" manufacturing.
V & VI General Comment	Subsection numbering would need to be appropriately changed. Since this reviewer rejects the previous comment because its basis rationale is fundamentally flawed, this reviewer suggests that the Agency simply ignore the commenter's contingent comment made here.	Provides continuity with previous comment. No continuity is needed because the commenter's previous comment is based on an obviously flawed rationale.
V. 203	We are unsure of what is meant by "uniform volumetric sampling" If this commenter is unsure about the meaning of this phrase, this reviewer suggests that this firm discuss this with their competent scientific staff who should understand the meaning of this scientifically well-understood phrase. Though this reviewer sees no need for this guidance to provide a meaning for the phrase, "uniform volumetric sampling," the Agency could add it to the glossary if they think that a definition is needed.	Clarification is needed. In a tapering blender, such as a ribbon blender or a conical blender, for batch-representative sampling, the sampling pattern should be adjusted such that the number of samples at a given level is proportional to the volume fraction at that level. [**Note:** In a cone blender being sampled at "4 levels," the appropriate pattern might be "7 samples" at the "top level," "5 samples at the next level down ("top down level"), "3 samples" from the level above the bottom level (bottom up level) and "1 sample" at the "bottom level" provided the volume ratios in the levels are approximately the same (7:5:3:1) as the number of samples at that level (7:5:3:1) – "uniform volumetric sampling."]

Section **G-Line**	**Comment / Observation**	**Rationale / Basis**
V. "224-229"	A clarification is needed to explain what indirect sampling means. We may want to add statements recommending when blend sampling is not possible e.g. Equipment (Blender design issues), Safety issues of sampling form the blender and/or IBC, density of powder bed makes it impossible to sample directly. This reviewer sees no need for a clarification of the term "indirect sampling" as it applies to sampling from the blender. In cases where sampling from the blender is, *because of scale*, not possible, the correlation between the active uniformity results from the IBCs to that of the blend samples from the largest-scale blender of that type that can be directly sampled can be established. Then the correlation between the active uniformity results from those intermediate-level IBCs to the corresponding results from the full-scale IBCs can be used to indirectly establish the active uniformity of the blend in the blender that, because of size, cannot be directly sampled. *If the Agency thinks that clarification is needed for what "indirect sampling" means*, the Agency is welcome to use this reviewer's remarks as a basis for providing the required clarifications being requested.	Definitions of alternate means of sampling may be necessary for clarification for when it may be impossible to directly sample the blend. First, the commenter's rationale is, at best, misleading because it changes the focus from the meaning of "indirect sampling" to "definitions of alternate means of sampling" – an altogether different issue. Second, the commenter's statement "… makes it impossible to sample to sample directly," indicates that, since the commenter does know what "sampling directly" means, the commenter also knows "what indirect sampling means." Isolators and robotic samplers make it possible to "sample the blend" in all cases though the routine full-scale sampling may need to be from the IBCs into which the blend is transferred after the blending operation is complete. The safety issue is a red herring in that isolators and robotic samplers make it possible to sample from even the most toxic materials. Moreover, this reviewer is well aware of the need for the personnel to work with isolators and/or wear the appropriate protective clothing including full suits with independent breathing air feeds (and has even designed a Level-4 Hazardous Chemical Handling Laboratory and worked with chemicals so acutely toxic that he was frequently tested for evidence of exposure).
VI. "239"	Change the word "criteria" to the word "classification". This reviewer does not agree with the commenter's suggestion here. However, this reviewer does recommend changing this sentence to read, "You should complete the assessment of powder mix uniformity and ~~correlation~~ **comparison** of **the final blend results obtained with the results from the batch-representative** dynamic in-process dosage unit sampling development procedures before establishing the criteria and controls for routine manufacturing." The preceding changes should be made to improve the accuracy of the statement being made and to correct the sampling plan to a batch-representative dynamic sampling plan that meet the applicable CGMP requirement set forth in **21 CFR 211.160(b)(2)**.	Provides clarity in describing the actual intent of this document. The proper intent of this draft guidance for the assessment of uniformity should, *because the Draft only addresses the active in the final blend and the dosage units*, be to provide guidance for a manufacturer for compliance with all CGMP requirement ***minimums*** for in-process final blends and in-process formed dosage units produced in the manufacture of the drug product specifically to the assessment of the uniformity (**21 CFR 211.110(a)**) with respect to the active. Based on the preceding realities, the commenter's rationale does not properly characterize "the actual intent of this document." Finally, all Agency guidance must conform to the binding regulation's ***minimums***.

Section **G-Line**	**Comment / Observation**	**Rationale / Basis**
VI.A. "250"	Add to the statement: "Carefully identify locations throughout the compression or filling operation to sample in-process dosage units, based on the results of development studies when available." This reviewer cannot support the commenter's addition because it changes the text's meaning but does not provide clarity. To provide the clarity this commenter requests, this reviewer suggests: "*Prior to the manufacture of the batch,* carefully identify ~~locations~~ **sampling *points*** throughout the compression or filling operation to sample in-process dosage units, based on the results of ***the scientifically sound and appropriate*** development studies performed. **Your selection should be done in a manner that ensures the points selected,** **a. Encompass the dosage-forming phase of the manufacture of the batch and** **b. Are sufficient to capture the variability across the batch**."	Provides clarity. Contrary to the commenter's rationale, the commenter's suggestion simply changes the meaning of the statement to permit location choosing to be done arbitrarily when no development studies are available (i.e., without a scientifically sound development study). If clarity is what the commenter is seeking, then the text should require such studies as well as correct the statement's "locations" to "sampling points" or "sampling time points." Similarly, to be clear, the text should specifically address development studies and the selection of the appropriate sampling frequency.
VI.D. "313-314"	We suggest the following clarification be added at the end of the paragraph: "It is acceptable to use 10 locations as long as they include all of the locations shown to potentially have an affect (sic) on quality during the assessment." The is reviewer cannot agree with any part of the commenter's suggested addition here even if the correct word "effect" had been used in place of the incorrect "affect." Since the guidance provided only focuses on dynamic sampling for the dosage units and to conform to the requirements of CGMP (as required by law), this reviewer recommends the following alternative: "You should identify **and designate** ~~at least~~ ~~10~~ **not less than 10 'routine production'** sampling ~~locations~~ **time points (the start point, the end point, and not less than 8 approximately evenly spaced intermediate points)** during capsule filling or tablet compression ~~to represent~~ **that your studies have established to be *representative of*** the entire routine manufacturing **of the formed units that comprise the** batch **while making provision for the inclusion of any 'significant events' that may occur during this production step. In addition, the number sampled at each point should be appropriately adjusted to be that integer multiple of all of the dosage forming stations in the forming system that is required to satisfy all of the firm's pre-established sampling and sample evaluation (examination and testing) for the said formed units**."	The USP content uniformity (CU) test requires 10 dosage units for evaluation stage 1. During routine production exactly 10 locations should be acceptable, since any more than 10 would make evaluation of the USP CU test confusing. The commenter's rationale is based on a false premise. Factually, the **USP**'s CU test is not appropriate for use under CGMP as it is not based on a *statistical sampling plan* that ensures the samples tested are a *representative sample* from the batch nor that provides a sufficient number of samples for production-scale batches (where the general minimum number that should be sampled is not less than 200 batch-representative units and, provided "REDUCED" inspection is justified, NLT 50 batch-representative should be evaluated initially provided a 95 % confidence level is adequate for the drug product (**see** the recognized applicable consensus standard **ANSI Z1.9**). Moreover, if the dosage-units' active-level results data is used for release, the CGMP regulations explicitly require statistical quality control be used (**21 CFR 211.165(d)**). [**Note:** Since from what the commenter has stated, it seems to be apparent that this commenter is using **USP** CU for batch acceptance for release even though doing would seem to be clearly proscribed by **21 CFR 211.165(d)**. This is the case because the **USP** CU test does not meet the clear batch acceptance for release ***minimums*** set forth in **21 CFR 211.165(d)**.]

Section **G-Line**	**Comment / Observation**	**Rationale / Basis**
VII. "319-321"	Suggest the following wording: " After completing the procedures described above, it is recommended that you evaluate routine manufacturing batches using the following criteria:" This reviewer opposes the change proposed by this commenter.	Provides clarity. The commenter's suggestion does not provide clarity, it changes the meaning of what the Draft states by eliminating the critical requirement to first complete the procedures outlined in the previous sections of the Draft.
VII.B. "394-398"	If the test results during routine manufacture fail the criteria, we disagree that "you should no longer use the verification testing methods to ensure adequacy of mixing or uniformity of content until you investigate the failure (per 21 CFR 211.192) to establish justified assignable cause(s), take the necessary corrective actions and repeat the powder mix assessment, stratified sample correlation, and initial criteria establishment procedures." *Though this reviewer recommends improving the wording quoted by this commenter*, this reviewer supports the general tenor of the text in the Draft and rejects the commenter's position. When a batch fails, in addition to starting an investigation into that batch's failure, the firm must also investigate all associated batches, released or not. Moreover, any scientifically sound CGMP-compliant inspection plans (the CGMP's sampling plans and test procedures) must include a switch to more intensive inspection whenever there is a real failure of a batch and, *when unexpected results are obtained*, also switch to more intensive inspection whenever this unusual pattern occurs. [**Note:** The consensus standards (ANSI Z1.9 and ISO 3951) provide a simplified discussion of this in subsection entitled "**NORMAL, TIGHTENED, AND REDUCED INSPECTION**."]	Judgment should be used to decide what the appropriate action is that should be taken on subsequent batches made during the period that the original failing batch is being investigated. A general statement meant to fit all cases is not appropriate. Since the Draft is guidance, a "general statement meant to fit all cases" is not only appropriate but also expected, because the general statement states what both CGMP and sound inspection science require. See the consensus standards' (ANSI Z1.9 and ISO 3951) subsection entitled "**NORMAL, TIGHTENED, AND REDUCED INSPECTION**."] Since this Draft is a guidance document, it compels nothing. Moreover, under CGMP, the judgment permitted to the manufacturer is exactly how to meet the clear requirement *minimums* stated in the regulations – compliance is required and knowing non-compliance subjects those who do to the risk of prosecution under the appropriate statutes as well as renders any batches produced in a non-complying manner adulterated. [**Note:** Based on the commenter's remarks, the commenter is either unaware of the regulations and thus unqualified under CGMP (**21 CFR 211.25**) or supporting the knowing non-compliance with the CGMP and, if this is the case, conspiring to subvert the regulatory process.]

Section **G-Line**	**Comment / Observation**	**Rationale / Basis**
VII.B. "398"	The guidance should The guidance should make the same statement that it does in lines 304-305 (but replacing the words "marginally pass" with the words "MCM") to read "The disposition of batches of batches that have failed the MCM criteria is outside the scope of this guidance." While this reviewer has no problem with replacing "*marginally pass*" with "MCM" in lines "304-305," this reviewer suggests that, to conform with the CGMP regulation minimums, the passage in question be modified to read: "If your test results meet these criteria, ~~results~~ the *batch* can be classified as ~~*marginally pass*~~ **MCM with respect to the active's uniformity**. If your samples do not meet these criteria, we recommend that you investigate the failure, find justified and assignable cause(s), correct the deficiencies, and repeat the powder mix homogeneity assessment, in-process dosage unit sampling ~~correlation~~ comparison, and initial criteria establishment procedures. The disposition of batches that have failed the ~~*marginally pass*~~ **MCM** criteria is outside the scope of this guidance. **However, because these are <u>not</u> "*passing*," the CGMP regulations in 21 CFR 211.110 clearly require such materials to be rejected (21 CFR 211.110(c)** 'In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, …,**') and quarantined (21 CFR 211.110(d)**, 'Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.**') <u>until</u> their deficiency or deficiencies can be corrected.**" This reviewer then proposes that a similar revision should be made for **Lines 392-399**.	The relevance of this statement seems to be just as true for line 398 as it is for lines 304-305, where the statement is included. We assume it's just an oversight. This reviewer agrees that what is true for the preceding text should be true here. To this end, he has proposed CGMP-conforming corrective language for the preceding passage that may be appropriate here. **Batch Acceptance Criteria:** This reviewer also notes that the Draft failed to mention, much less address, the issue of establishing valid ***acceptance criteria*** (**21 CFR 210.3(b)(20)**) for the ***batch*** based on the results found from the testing of a small percentage (currently, less than 0.2 % and in an increasing number of cases less than 0.02 %) of the batch even though such ***acceptance criteria*** are clearly needed and, for the drug product units tested for acceptance for release, are explicitly required (**21 CFR 211.165(d)**). **After all, it is the untested part of the batch that the patients will be prescribed.** To address the Draft's omission, this reviewer has included corrective language for the prior passage that should be appropriately reflected here. [**Nota Bene:** In addition, *as noted in a previous review (of PhRMA's comments)*, the entire inspection plan proposed is flawed and, as this reviewer has outlined, needs to be appropriately "corrected."]
VIII General Comment	Summaries of data will not always be available at the time of filing. We suggest that it be submitted only if available. *While this reviewer agrees that the information from the initial full-scale conformance batches produced for the initial process "Performance Qualification" confirmation of process reproducibility*, to submit an application, the manufacturer is supposed to have fully developed their drug product processes, including production of at least one (1) process conformance demonstration batch. When the preceding has been accomplished, then all the information needed should be: **a)** available before a submission is filed **and b)** filed with it. Therefore, this reviewer <u>cannot</u>, in good conscience, agree with the commenter's suggestion here.	This commenter failed to provide any rationale here. If needed data is <u>not</u> available, the firms should withhold their filings until such time as the requisite data, including that data required to assess the uniformity of all critical variable factors, including, but most certainly not limited to, active level is available. [**Note:** <u>Unless</u> the commenter's intention is to admit that they submit processes that they do <u>not</u> know are valid and well-controlled for FDA review and approval with the hope that, *after approval*, the production process may consistently produce acceptable batches that meet the CGMP ***minimums*** with the knowledge that their hope may <u>not</u> be realizable – an apparently clear subversion of the regulatory process, the commenter's should reconsider what is being said here.]

Section **G-Line**	**Comment / Observation**	**Rationale / Basis**
Attachment 1 "491-503"	A company should be allowed to pass blender S1 criteria with n=30 if it fails S1 criteria with n=10 before requiring investigation of original S1 criteria "failure" and determination of whether there is a mixing problem. *Since the fundamental approaches in the published draft do not conform to the clear applicable CGMP **minimums** for in-process materials and in-process drug products*, this reviewer must reject the commenter's flawed comments and again request that the Agency first correct this guidance until its language conforms to the clear applicable CGMP ***minimums*** for *in-process materials* and *in-process drug products* including the regulation ***minimums*** set forth in **21 CFR 211.110**, **211.160**, and **211.165**.	S2 should have an acceptance criteria and not just a general requirement to determine if there is a mixing problem. Meeting S1 blender criteria with n-30 should be satisfactory demonstration that there is not a mixing problem. If not met at S2, then we believe the investigation is then necessary. While this reviewer agrees that there should be appropriate *acceptance criteria* for the samples, there should also be appropriate *batch acceptance criteria*, but none have been proposed in this draft guidance. This is but one clear example of the draft guidance's failure to conform to clear CGMP requirements – enough said.
General comment	We believe it is not practical to require a new validation for all existing products where the original validation was not performed as stated in this guidance. Some additional guidance is needed. If an existing validation can be shown to be at least as discriminating as the guidance and it meets either the readily pass or marginally pass, we feel that this would be satisfactory justification for using this guidance criteria for routine manufacture. In addition, if we have satisfactory blender test results (as per guidance document) but, while acceptable, we can't demonstrate that the existing validation data for in-process dosage units is at least as discriminating as that of the guidance, then we feel that that as a worst case, one should be allowed to pick up routine testing using MCM sampling and criteria requirements and switch to SCM criteria after meeting the switching rule criteria for switching. This reviewer disagrees with the commenter because CGMP compliance is required and neither the Draft nor the commenter's remarks conform to the clear applicable CGMP minimums.	As long as we have demonstrated no mixing problem, this approach would use the more conservative criteria and larger sample size associated with the MCM criteria for routine production until the switching rules would allow switching to the SCM criteria. Since the commenter proposes no scientific definition of what constitutes demonstrating "no mixing problem," this reviewer cannot form a cogent response to the commenter's rationale statements here. However, instead of focusing on what, to any knowledgeable person, are obviously non-CGMP-compliant practices, the Agency and the industry would be better served if the commenter focused on providing CGMP-conforming guidance that: a. Clearly conforms to all applicable CGMP requirements for in-process final-blend materials and in-process drug products that this draft guidance purports to address, b. Addresses the requirements for those other critical variable factors in such materials and products, c. Speaks to the in-process materials produced by significant phases before the final blend (e.g., pre-blend, granulation, component or active conversion to a compressible form) phase.

"Attachment 2
'PDA Comments"

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
General Comment	The guidance avoids the term 'validation', using less descriptive titles like "verification of manufacturing criteria". We recommend including the term 'validation' and 'development' to clarify the purpose of various sections. First, though the phrase "validation process" is not used, the word "validation" appears eight (8) times in the body of the Draft so it is less than fair to claim the guidance avoids the term "validation." Based on the commenter's recommendation, it would seem that the commenter's real concern is that the titles do not use the terms "development" and "validation" when, in light of the recent revisions to FDA **CPG 7132c** in **Sec. 490.100**, "Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08)," official as of 12 March 2004, this commenter should have realized why the Agency avoided the use of the term "validation" in the titles of the sections in this drug product[1] guidance. Moreover, because this guidance is intended to apply generally, it is inappropriate to use the word "development" in the section titles because that word carries with it the connotation of an activity limited to new products when the draft guidance provided is clearly intended to be guidance applicable to all products. [1] **21 CFR 210.3(b)(4)**, "Drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo."	The PQRI proposal clearly defines activities that are performed during development (pre-validation) and validation. The reluctance to use the term validation creates a disconnect with the PQRI proposal and makes the draft guidance more difficult to interpret. When addressing validation, the cited Agency CPG states (emphases added): "**Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110)**, and is considered an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs) under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. *A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product. The* ***proof of validation is obtained*** *through rational experimental design and the evaluation of data*, preferably **beginning *from* the process development phase** and **continuing *through* the commercial production phase**." Based on the preceding, ALL such "drug product" batches are "validation" batches as per **21 CFR 211.110(a)**'s "control procedures shall be established to monitor the output and **to validate** the performance of those manufacturing processes that …" for each batch and its use to differentiate between phase would, in light of this policy and the cited regulations, therefore be futile. The basis for not including, the word "development" in the section titles is explicitly addressed in this reviewer's observations. Moreover, under **21 U.S.C. 321g(1)**, *that defines a drug*, all "development" batches that are administered to humans or animals are drug product batches upon which firms must use control procedures "to monitor and validate …" **21 CFR 211.110**. Thus, the PQRI's understanding of CGMP is, at best, flawed.

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
General Comment	If, through development, we know that reliable blend sampling is unattainable (up to 10x) due to thief error and we have data to prove this, do we still need to pull blend samples during validation or can we skip sampling from the blend in validation and use Stage 2 dosage unit testing to demonstrate uniformity of the blend. This reviewer finds the commenter's proposition here represents a clear example of scientific psychosis to all who understand the fundamentals of material inspection as these apply to complex blends of solid powders. In general, *when you have sampling problems*, at any level, you should: • First, identify the primary causes for the problem (component specification control issues, mechanical instability of the blend, sampling tool design, sample amount, and/or sampling technique). • Second, minimize or eliminate the cause or causes of the problem (improve the controls on the components, uniformity and/or mechanical stability of the formulation, sampling tool design, sampling amount, and the minimally invasive sampling techniques until these sampling problems are minimized of eliminated. • Third, after the sources of the "sampling problem(s)" have been identified and corrected, perform inspection (sampling and testing) on sufficient blends to verify that there is no significant residual sampling bias. • Fourth, finalize the controls and procedures used in Specifications, SOPs and Work Instructions as appropriate. • Fifth, implement the proven procedures in all further studies. When the batch blend's volume reaches the size that precludes the taking of a *batch-representative* set of unbiased "mixer" samples of an amount sufficient for all replicates for all critical variable factors that require an independent sample work up, migrate your blend sampling point to the IBCs into which the blend is transferred after blending. [**Note:** In general, *for near-full-scale blends*, the sample amounts required for an unbiased sampling from each sample location are on the order of 10's of grams even though the unit-dose sample sizes for the testing are on the order of 50 to 1000 milligrams.] --- Efforts to get vendor to provide free-flowing grade that met firm's particle-size specifications and the proposed flow specifications (derived from study on the retains from previously acceptable API lots) were <u>not</u> successful. Firm ceased manufacture of this drug product because root cause of the problem (API flow) could <u>not</u> be resolved (API source uncooperative).	Continuing to use a flawed test would not add meaningful data to the Validation exercise. This does not remove the obligation of the firm to use good science to continue the search for more robust sampling methodology. While this reviewer agrees that it is folly to continue "to use a flawed test," this reviewer knows that, as the commenter states, "the obligation of the firm to use good science" is an absolute obligation that must be met. However, the commenter's proposal accepts as "gospel" that the root cause for the "blend sampling" problems is in the tool or technique used when, *based on this reviewer's experience*, the "root causes" are most often in the formulation or formulation processing operations or, almost as often, sub-standard or missing controls on one or more components. Thus, though it is all too easy to blame the sampling tool or technique rather than a sub-standard formulation or sub-standard component controls, as the commenter's remarks clearly indicate, this reviewer counsels that the root cause(s) for the "blend sampling" problem found must be identified and appropriate root-cause-corrective actions taken. Two illustrative examples readily come to mind. **Blending-Related Non-Uniformity** *In development of a direct blending process, the firm put a blue dye in "10 mg" strength of the formulation and a yellow dye in the "20 mg" strength to differentiate them from each other even though the weights of the tablets were proportional.* *Using the lab formulation procedure developed without the dyes), the studies found the "0.1 % yellow dye" final blend was uniform but the "0.09 % blue dye " one was not.* *A microscopic examination on small-scale blends found that, relative to the dye-free blend, while the <u>yellow dye</u> used <u>promoted</u> blend <u>uniformity</u>, the <u>blue</u> dye <u>caused</u>* active <u>agglomeration</u> that prevented uniformity from being achieved. The problem was "solved" by changing the dye used to a different one that did not trigger agglomeration of the active. **Component-Related Non-Uniformity** Approved process that had "no history" of significant problems (based on CU testing "suddenly" experienced multiple uniformity problems found in released batches by FDA. Investigation found root cause was a fundamental change in the flow properties (for which the firm had no specification) of the active. (Continued in adjacent column ←)

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
58	The following lines are suggested for inclusion in the Scope: "After Readily Passing all validation batches, products that are allowed to meet USP requirements using content uniformity by weight variation are exempted from future routine blend testing requirements." This reviewer cannot agree with the commenter's proposal because it ignores the clear applicable requirements of the CGMP regulations that bear on in-process materials and in-process dosage units for each batch of all drug products. Moreover, this reviewer is at a loss to see how the **USP**'s discrete dosage-unit requirements can be directly applied to the non-discrete final-blend samples. In addition, this reviewer notes that this draft guidance deliberately and improperly ignores: • **USP**'s expectations for the range for the content values found not more than (NMT) 1 in 30 outside of 85 % to 115 % of the **USP** target for "tablets" and, for capsules, NMT 1 or 2 in 30 outside of 85 % to 115 % of the **USP** target for "capsules." • Explicit ***General Notices***' requirement that the mean found must be "100 %" of the label claim or **USP** Assay's mid-range value, and • The explicit **USP** "blend (from which the dosage units were formed) is uniform" assumption contained in the **USP's** *Uniformity of Dosage Unit* test procedures.	The PQRI report to the FDA recommended the exclusion from the requirements of the guideline those products where the determination of dosage0-form uniformity by weight variation is allowed. The former BU draft guidance for ANDA products also excluded these products. Again, the PQRI shows it lack of understanding and deliberate disregard for the applicable CGMP regulations governing in-process materials and in-process drug products. By law, the **USP**'s procedures ONLY apply to released drug product batches in commerce. Moreover, because they do not require *batch-representative samples* nor, *in the case of the dosage units*, do they test sufficient dosage units to meet the clear requirement minimums of the applicable CGMP regulations, nor, for that matter, the recognized number minimums set forth in the applicable consensus standards (which are designed to provide a 95 % level of confidence that the sample results are predictive of the active content properties of the batch) for the "process variability unknown—standard deviation" case which clearly applies to dosage units produced from components that do not even identify, *much less rigorously control*, the critical physical properties for all components and materials used to manufacture said dosage units. [**Note:** In general, the maximum **USP** number, 30 units, even if taken from a *batch-representative sample*, provide batch uniformity estimates that can only predict the batch's active uniformity at a confidence level that is less than 20 %.]
95-97	Remove sentence, "Formulations with extremely low dose and/or high potency may call for more rigorous sampling…units. This reviewer does not concur with the commenter's suggestion because the sentence states a factual reality. Therefore, this reviewer strongly recommends that this sentence be retained in the final guidance.	Sentence is ambiguous in that it calls for more rigorous sampling, but gives no guidance or reference to how to accomplish these ends. The sentence is not ambiguous; it clearly calls for more inspection when the level of active is extremely low. That it does not prescribe what should be done is appropriate because the proper course of action depends upon: **a)** the level of the active and **b)** its uniformity in the final blend.

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
108	For clarity: Change the section title so that it clarifies that these exercises are Development (pre-validation) procedures. One possibility" "IV. Evaluating Powder Mix and In-Process Stratified Sampling During Process Development" Though this reviewer cannot agree with the commenter's suggested alternative, this reviewer does agree that this title should be revised. Based on the commenter's input, this reviewer suggest the title be changed to: "IV. **Establishing Sound In-process Active Uniformity Specifications For the Various In-Process Non-discrete Materials, Including the Final** ~~Evaluating~~ Powder Mix, and the **Discrete In-Process Dosage Units Produced** ~~Stratified Sampling During Process Development~~" **From the Non-Discrete Final Blends**	It is not clear (to all readers) that this is a separate procedure from that proposed in Section V. A title and purpose statement will help clarify the reason for the difference in sampling scheme and lack of acceptance criteria. Properly, this section should address the issue of setting *scientifically sound* and *appropriate specifications* for each non-discrete in-process material and the in-process drug-product units produced by a given drug product process and not, as the commenter's suggested title indicates, activities that are exclusively associated with process development. Moreover, the title suggested by the reviewer clearly indicates that this section of the Draft addresses the setting of *specifications* for each active-containing in-process material (not just the "final blend" from which the dosage units are formed) and the discrete in-process formed dosage units for active uniformity – one of several critical variable factors that must be appropriately controlled and evaluated in each in-process batch of drug product. Titled as this reviewer suggests, the purpose of this section should be clear to all.
123	Add a 'purpose statement' to this line. For example: "As a part of development, we recommend that you assess critical events in the blend process and determine appropriate sampling techniques for demonstrating a validated blend process. As a part of this evaluation, we recommend the following procedures." This reviewer does not agree with the commenter's suggestion because it falsely asserts that the reason for the added wording is "for demonstrating a validated blend process," something that, because validation is, *as the Agency clearly recognizes and the in-process CGMP regulations specify*, an ongoing "each batch" journey and not a destination, as the proposed text implies. Provided the guidance is restricted to the assessment of active uniformity, this reviewer offers the following: "As part of specification development, we recommend that you establish that each of your: **a)** Discrete-material sampling plans produces unbiased samples sufficient in amount for all evaluations and **b)** Test procedures appropriately samples and evaluates duplicate unbiased unit-dose, or smaller, sample aliquots from each sample so that you can thereby prove the validity of the results you obtain. As a part of these procedures, we recommend that you use the following procedures to assess the uniformity of each active in each non-discrete active-containing material produced by the drug-product manufacturing process you are evaluating."	Clarify, to help others understand the importance of the section. **21 CFR 211.110(a) –** the clear "each batch" "to monitor … and to validate …" requirements contained therein clearly establish that validation is a journey and that no process that is being used can properly be considered to be validated – at best such can be considered "valid" or "supporting the validity of the overall process." **See also**, the discussion on validation contained in Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08) of the FDA's Compliance Policy Guide 7132c effective 12 March 2004.

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
146	Add a 'purpose statement' to this line. For example: "Prior to validation, we recommend that you assess the in-process dosage unit data to identify locations throughout the compression/filling operation that have a higher risk of producing failing finished product uniformity of content results and to identify the stratified sampling that may be used to verify powder mix uniformity. We…" Though this reviewer has no objection to adding a "purpose" statement, This reviewer finds the commenter's suggested text is both at odds with the principles of validation and unrealistic. Until the flawed guidance offered is corrected in a manner that fully conforms to the applicable requirement minimums of the CGMP regulations this reviewer cannot recommend appropriate wording. However, this reviewer notes the following problem areas that should be addressed by the Agency: 1. The multi-level analysis of the final blend material in the IBCs used to charge the feed to the dosage forming equipment 2. Sampling a *representative* number of units from each dosage-forming station at each sampling point. 3. Evaluation of a *representative* subset from each sample sampled from the in-process dosage units. 4. Linking the uniformity of the material in each IBC to the uniformity of the dosage units formed from it, 5. Restricting the guidance to the uniformity of the active or actives present.	Clarify, to help others understand the importance of the section. *Since most recognize that validation begins in development and labels that phase as the Design/Development Qualification phase (DQ)*, the actions suggested here fall within the validation envelope. *Unless the guidance provides some mechanism (like the one suggested) to link the results from the some part of the final blend to the results for the dosage units produced therefrom*, there is no way to effect the identifications suggested. *Unless the guidance is restricted to the uniformity of the active or actives*, measuring active level does not address or ensure overall uniformity. *Because dynamic sampling is the sampling used*, the failure to require the taking of at least one unit from each dosage-unit-forming station at each sampling point fails to ensure that the samples sampled are *representative* of the batch. *Under the present scenario*, all that can be compared is an uncertain final blend's active uniformity based on biased samples to a non-representative-sample-based even less certain estimate of the active uniformity in the formed dosage units sampled. *Under the Draft's scenario*, the weight-corrected active content values computed from the biased dosage results are biased estimates of the variance of the blend plus variance of the transfer operations, the variance introduced by the dosage-unit-forming process, and the lumped error variance.

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
160-161	Change lines 160-161 to read "Prepare a summary of the data (and analysis), identifying the significant events in the manufacturing process that may impact blending and from this, identify the stratified sampling that may be used to verify powder mix uniformity. We…" This reviewer does not support the commenter's suggested wording for the cited text for the same reasons as he has presented previously. Provided the draft is restricted to only assessing the uniformity of the active or actives and the text is modified to require the in-process dosage units evaluated to be not less than 200 batch-representative units (for "NORMAL" inspection) and the results composed of the values found for an equal number, chosen at random, from each routine sampling point and any additional sampling points, this reviewer suggests the following alternative: "• Prepare a summary of the data including the specific content values (content values corrected to the target unit or unit-fill weight) for each tablet tested and the corresponding statistical estimates derived therefrom, minimally at the 95-% confidence level, and compare those statistical estimates to the corresponding statistical estimates for the active level in the final blends." 8. Compare the results from each IBC to the weight-corrected results from the tablets linked to the IBC. 9. Compare the statistical estimates of the batch result limits for the blend to those from the in-process dosage units. 10. Enter all results into an appropriately constructed table. 11. Use the appropriate statistical analysis procedures and a confidence level of not less than 95 % to analyze all of the data and generate appropriate findings as to the predicted active uniformity of the blend and the in-process dosage units as well as the relationship, if any between IBC results and the related in-process dosage units. 12. Report all data and findings. [**Note:** If the active's variance for the in-process dosage units is significantly larger than that for the blend, investigate and, once the cause has been found, take corrective action.]	To clarify purpose and prevent some confusion over the use of the term 'correlate'. Comparing biased estimates of the blend's active uniformity from a few singlicate (ca. 20) non-representative blend results with no local estimate of result reproducibility to the in-process dosage-units' active uniformity from a few (ca. 140) non-representative dosage-units' results that are, at best, weakly linkable as in the Draft's scenario is a less than scientific procedure. If the guidance is restricted to active uniformity and, in development, the guidance should direct that you should: 1. Sample unbiased samples from multiple levels in each of the IBCs from the final blend and perform duplicate aliquot tests (with at least two measurements on of the active in each aliquot) on each sample from each IBC in a manner that links the results to the location in the IBC location from which it came. 2. At not less than 20 sampling points across the production of formed dosage units, take not less than four (4) dosage units for each dosage-unit-forming station *at each sampling point, "routine"* ("start," "n time point," and "end") and "*significant event"* (e.g., restart, hopper rundown), and collect each in a separate, appropriately labeled container, 3. At each sampling point note the IBC container number and approximate level of the blend that is being formed until all samples have been collected. 4. From each "routine sample" sampling point container, take not less than ten (10) dosage units chosen at random from that sampling point and label the test-sample container with its sampling point ID. 5. At each "significant event" sampling point container, take not less than ten (10) dosage units chosen at random from that sampling point and label the test-sample container with its sampling point ID 6. Weigh and analyze all samples in a manner that provides at least two valid measurements for each dosage unit and preserve all result, ID and weight links. 7. Compute the weight corrected active level for all active level results. (← Continues in the adjacent column)

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172-185	Reformat for clarity: Move this section under the topic of Section VI, with the additional option that if this verification has previously been completed in development, that it is not necessary to repeat the evaluation. This reviewer cannot agree with the commenter's suggestion here as it flies in the face of both common sense and sound science. If you cannot find in development that the uniformity of the active content in the freshly formed dosage units is comparable to the uniformity of the active in the finished dosage units in all the development-related batches, either the process in question falls outside the scope of this guidance (e.g., more of the active is added in one or more coating steps) or, if the drug product definitely falls within the scope of this guidance for assessing the uniformity of the active, your product development activities have, to date, been inadequate. However, the guidance furnished in the Draft clearly conflicts with many of the requirements set forth in **21 CFR 211**. Therefore, this reviewer again strongly suggests that this section of the guidance be revised until it conforms to all of the applicable requirement minimums set forth in the CGMP regulations.	Most companies will use the extended testing during validation to compare in-process to finished product, in order to obtain better estimate. During development, it may not be practical to obtain a sufficient amount of data to demonstrate equivalency or 'correlation' between final and in-process product. It should be obvious that a drug-product falling within the true scope of this guidance (*assessing the uniformity of the active or actives* in the in-process materials and the drug product [a single-layer, single fill tablet or capsule made from a single uniform final blend]) must have an active uniformity in the freshly formed dosage units that is comparable to the active uniformity on the finished dosage units tested for release for distribution (for each active) or the process development needs to be continued or restarted. However, the guidance in this section does need significant revision to ensure that sufficient batch-representative drug-product samples are appropriately evaluated against scientifically sound and appropriate specifications which ensure that all of the untested units in the batch will, after the batch is released, meet the **USP**'s "in commerce" requirements. If the uniformity of the active is the only aspect of the assessment of the uniformity of the drug product, the minimum number of drug-product samples that must be tested is on the order of 200 (the minimum number that should be tested is on the order 300 to 900 representative units depending upon the level of confidence required for setting process' projected limits and initial specifications). The scientifically sound and appropriate acceptance criteria should be derived from those established in the recognized consensus standards for the inspection of variable factor for the percent nonconforming published by ANSI and ISO. This is the case for drug products because, *for release*, the drug product dosage units must meet the requirements set forth in **21 CFR 211.165(d)**.

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174	Add a purpose statement to this line: "In order to use in-process samples to fulfill the compendial uniformity of dosage unit requirement for finished products, we recommend the following steps:" This reviewer cannot agree with this commenter's statement because it is not factually true. The clear applicable CGMP requirement minimums, and not the **USP**'s post-release ones, are the legal binding requirements that, *under law*, each manufacturer must use to assure that *each batch* (of drug product the manufacturer accepts for release into commence) is not adulterated as that term is defined in **21 U.S.C. 351(a)(2)(B)**.	It is currently unclear why this section is important. The commenter's'' remarks do little to make it clear "why this section is important." Factually, there is **no** "compendial uniformity of dosage units requirement for finished products" ***prior to*** the ***release of*** the ***batch*** nor, for that matter, are the **USP**'s requirements applicable to other that the *post-release* "in commerce" *article*, as said *article* is defined by the **USP.**
216 (revised)	The following revision of the revision suggested: If the samples do not meet these criteria, we recommend that you investigate the failure according to the flow chart in Attachment 1. Assay the remaining replicate blend samples. To aid in investigating the cause of failure, dosage from samples (seven form at least 20 locations) may be analyzed. These samples should have been obtained following the procedures described in Section VI, Verification of Manufacturing Criteria. If the cause of failure is not because of mixing, but is attributed to sampling error, or other problem(s) unrelated to the homogeneity of the blend, we recommend that you proceed with the evaluation of the dosage form data as described in Section VI. Because the CGMP regulations require *blend inspection* and *blend release* prior to the initiation of dosage formation and direct that *failing in-process materials must be quarantined* and withheld from use until an investigation can determine they are suitable for the step in which they are to be used, this reviewer cannot support the commenter here. In addition, the suggested course of action is at odds with the fundamental precepts of the "cost of quality" that counsel investigation and appropriate corrective action before you proceed with the manufacturing process. In addition, this reviewer cannot support the guidance proposed because, as published, it does not take a *batch-representative set* of *unbiased samples* of an amount in excess of three times the amount needed for the evaluation, in duplicate, of all of the critical variable factors in the final blend or evaluate unbiased duplicate aliquots from each sample for the level of active(s) in each sample sampled. Until this guidance's fundamentally flawed approach to blend sampling and blend-sample evaluation is corrected, this reviewer sees no value in commenting further about the Draft's present sampling plan or the equally flawed scheme associated with it. (Continued)	Attachment 1 needs to be slightly revised to conform to this change in wording. The box containing the text, "Assay at least seven dosage units per each location, weight correct each result" should be moved to be just under the box containing the text, "Assay 2nd and 3rd blend samples from each location" If you have truly identified and controlled all critical sources of variability, this reviewer, the Agency, and other scientists who understand the development of drug-product processes for tablets and capsules expect that failures of the valid active content blend results to meet *any* of the blend's ***scientifically sound*** and ***appropriate sample*** *specifications* and *batch acceptance criteria* should be rare. Sound inspection science for non-discrete materials dictates that each sample must be an unbiased sample that is larger than the amount required for a full test, retest and reserve for all the critical variable factors to be evaluated. In addition, for *batch-representative sampling*, the sample locations chosen must be proven, in development, to be sufficient to span the batch and include samples from all types of areas including the areas where development has established the "worst" and the "best" uniformity results for all critical variable factors have been consistently found in addition to areas where the blend consistently has been found to have similar uniformity with respect to all critical variable factors – not just to the active or actives in the formulation. To ensure that you can obtain valid estimates of the within-sample variability and to provide a check for possible analytical bias, this reviewer must recommend that each unbiased sample should have unbiased duplicate "unit dose" (or smaller" aliquots removed and evaluated.

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
216 (revised) (Continued)	(Continued) *Provided the inspection plan and decision schema are corrected in the manner suggested in this reviewer's previous remarks or a equally or more CGMP-compliant inspection-science conforming manner*, this reviewer suggests, as does the commenter, that finding of a failure should trigger an in-depth root-cause investigation designed to identify the root cause(s) of and the appropriate corrective actions for the failure observed. However, *because the sample-evaluation plan should include adequate safeguards (in the reviewer's view, duplicate "unit dose" aliquot evaluations with duplicate measurements of each aliquot) to ensure that, when an "analytical error" occurs, it should be detected before a result is certified and reported by the "laboratory" performing the sample analyses (and compensated for by evaluating an appropriate number of additional "unit dose" aliquots)*, this reviewer sees no need to address "analytical error" in this guidance as opposed to true result variability because in a CGMP-compliant laboratory the reported results should only be reported and acted upon when the laboratory has certified the accuracy of the results. Returning to the commenter's suggestions, this reviewer essentially agrees with the commenter and suggests that the revised guidance contain the following language: "Identify the root cause of the failure. If the root cause is a mixing problem, we recommend that you proceed no further with implementation of the methods described in this guidance until you develop a new mixing procedure." However, this reviewer cannot agree with commenter's suggestion when the root cause of the failure is identified as a sampling related error and recommends the following text: "If the cause of the failure is proven to be a sampling-related problem, then take whatever root-cause-corrective actions are needed to solve the sampling-related problem and, after you verify that the root-cause-corrective actions are both valid and effective, resample the blend."	(Continued) The upper limit on the evaluation amount in any material should be "unit dose" because that is the drug products' nominal unit of uniformity. However, when the tablet is scored and the dosing directions include the breaking the dosage unit into halves or thirds and taking half or one-third, you should seriously consider blend sampling at the "half unit dose" or "on-third unit dose" level. Further, *for high dose tablets where the 80% or more of the formed dosage unit is a single active and the dosage unit weighs 100 mg or more*, you may sample at whatever sub-unit-dose weight level that your development studies has found to provide accurate estimates of the uniformity of the drug product's uniformity and is optimal for minimizing the analytical uncertainty introduced by the procedure used to sample, work up, and evaluate the sample aliquots tested. Fundamentally, for non-discrete materials, it is scientifically sound and "doable" for you to sample large unbiased *location-representative* multiple-dose samples that are appropriately larger in amount than the amount required for all projected evaluations for all critical variables, handle those samples in a manner that does not introduce any significant post-sampling variability changes (positive or negative) into the sample, sample duplicate unbiased unit-dose or smaller aliquots from each blend, and work up and analyze the unbiased aliquots sampled. It is not scientifically sound for you to use a biased sampling procedure that repetitively samples biased "1-3 dose" amounts from ever differing locations from a less than batch-representative set of general locations and attempt to attribute any replicate sampling as being from the same "location" or claiming that the results from replicates in the same repeatedly disturbed general location are from the same "location" or to claim that, if necessary, you can go back and sample from the same location since every sampling changes the nature of the material in that "location." [**Note:** *Even if each sampling minimally disturbs the material in the location sampled*, then it should be obvious that a sound sampling plan that disturbs each location once for 2 tests for each of four critical factors is better than one that would need to sample each location no less than 12 times!]

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
"224-233"	Move section under V. 1. After the word risk in line 224 add "or physically impractical (example, large blender. This reviewer does not agree with moving Lines 225-235 in the published (to the Draft Guidance file) Moreover, this reviewer suggests the following alternative to the commenter's suggested change: "This section describes sampling and testing the powder mix of ~~exhibit and process validation~~*process conformance* batches used to support implementing the ~~stratified~~ sampling ~~method~~ *plans* described in this guidance. ~~Some powder blends may present unacceptable safety risk or be physically impractical (e.g., large V-blender) when directly sampled.~~In cases where the direct sampling from the blender presents an unacceptable risk for direct sampling or such sampling is physically impractical (e.g., the manufacture should justify and use and alternative procedure for monitoring and validating the uniformity and integrity of such blends. Unless the toxicity of the active presents an unacceptable safety risk to the persons doing the sampling and no isolator-contained sampling system or robotic sampler is available, these justified sampling alternatives should be to sample from the IBCs using the sampling guidance provided in **21 CFR 211.84(c)(4)** for the sampling of components as the *minimum* for the number of levels to sample from each container. In addition, as previously discussed, the samples sampled should be sampled, handled and subsampled (*aliquoted*) for testing in a manner that ensures that the samples tested are an unbiased set that is *representative* of the blend from which the sample set was taken. Each sample should be of sufficient amount to permit the testing of at least six (6) unbiased aliquots from it for each critical variable factor (active content, active availability, weight, identity, and, where indicated, water and other impurities) that was identified as having a significant variability in development studies conducted as per Section IV.A. ~~Once described, these situations may justify an alternative procedure. In such cases, process knowledge and data from indirect sampling combined with additional in-process dosage unit data may be adequate to demonstrate the adequacy of the powder mix. In such cases, the data analysis used to justify using these alternate procedures should be described in a summary report that is maintained at the manufacturing facility~~.	This section seems to describe the general practice of sampling. It would flow better if placed as suggested, where the guidance discusses locations of sampling. This reviewer notes that the section it is currently in also addresses the final blend (powder mix) Some blender installations due to size of the blender or room considerations do not lend themselves to safe or practical sampling in the blender. In such cases sampling from drums after discharge may be justified as long as location sequence is maintained. This reviewer does not disagree with the commenter here. However, for all of the valid regulatory and sound inspection science reasons established previously, this reviewer recommends that the commenter's suggestions be modified as indicated.

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
Amendment line number 260 (new text)	Change to "Conduct an analysis of the dosage unit stratified sampling data to assess the active ingredient distribution throughout the batch (e.g., visual assessment of a histogram or a probability plot). Indications of trends, bimodal distributions, or other forms of a distribution other than bell-shaped should be evaluated." Though this reviewer agrees with the commenter that this bullet point needs to be revised, this reviewer suggests it be changed to: "• Conduct an analysis of the dosage–unit ~~stratified~~ dynamic sampling ~~data~~ weight-corrected results to demonstrate that the results obtained for the batch-representative samples tested indicate that the dosage units in the batch probably ~~has~~ have a *near* normal active-content distribution ~~of active ingredient~~. At the simplest level, one can determine the mean, median and mode values for the data set – when they are, within the observed result uncertainty, the same, the level of active in the batch of tablets can be presumed to be normally distributed. If this simple test is inconclusive, then you should construct a frequency bar graph depicting the frequency of values in a given narrow value range interval on its "Y=axis" against the mean active level in the interval increments specified on the "X-axis," and examine this chart and the tabulation of the results versus time point. Indications of trends, bimodal distributions, or other forms of a distribution other than normal should be investigated. If any of these ~~occurrences~~ conditions significantly affect your ability to ensure batch ~~homogeneity~~ uniformity of the active(s), ~~they should be corrected~~ the root cause or causes for the non-uniformity of the results should be identified, appropriate corrective actions implemented, and the studies repeated until the results indicate that the batch is sufficiently uniform with respect to the level of active in the dosage units."	Actually, a unimodal shape or a bell-shape with short tails (high peak of data in the center) is not a normal distribution, but it is a preferred shape when describing batch uniformity. A normal distribution is acceptable, but not required. The commenter's rationale again misstates the reality that a normal distribution is the preferred distribution but that many near-normal unimodal or bell-shaped distributions are acceptable distributions where it is valid to use "normal" statistical procedures to describe the approximate dispersion of the critical variable factors' results about the calculated average value and predict the batch's dispersion of these critical variable factors, including the active(s) about the batch's targeted mean value. The critical caveats are: a. The samples tested must be *representative* of the batch and b. The number tested must be sufficient to provide a high level of confidence (typically, at the 95 % confidence level or higher) that the outcomes observed for the samples tested do, in fact, reflect the untested units in the batch. For the initial "full scale" conformance batches to which this procedure applies, the minimum number that should be tested is 200 batch-representative dosage units.
273	Change to "For each separate batch, compare the weight-corrected test results to the following criteria:" This reviewer cannot agree with the commenter's suggestion because it is at odds with the clear in-process CGMP requirements that require the active's dosage-unit uniformity to be evaluated on "**the characteristics of in-process material**" the weight-corrected active is NOT a characteristic of the in-process dosage units – it is a biased characteristic, and suggests the following CGMP-compliant alternative: "For each ~~separate~~ *individual* batch, compare the dosage-unit test results to the following criteria:" (Continued on next page)	Clarification for those not familiar with the PQRI proposal. **21 CFR 211.110(a)**, "…Such control **procedures** shall be established to **monitor the output and to validate** the performance **of** those manufacturing **processes** that **may be** responsible for **causing variability in the characteristics of in-process material** and the drug product. All that the *weight-corrected formed dosage-units active-content results* should be used for is to compare the *weight-based blend results* to the *weight-corrected formed-dosage units results* in instances where such comparisons are valid – this is clearly not the case here. (Continued on next pages)

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
"273" (Continued)	(Continued) In addition, the rest of this section (Lines 276-285) should be revised to: "• For all individual results **for each active individually** (for each batch**,** n ≥ ~~60~~ **200**)**,** the overall RSD ≤ ~~4.0~~ **2.5** percent." • "For all individual results **for each active individually** (for each batch**,** n ≥ 200)**,** the overall mean percent of the target value should be not less than the target value percent. In practical terms, this requirement translates into: **$[\bar{x}_n + (t_{(0.975,n-1)} \times RSD / \sqrt{\{n-1\}})]$ % ≥ Target Process %.** • Each ~~location~~ sampling-point mean is within the relative range of ~~90.0~~ **≥ 93.0** percent to ~~110.0~~ **≤ 107.** percent of target strength. • All of the individual results are **appropriately** within the relative range of ~~75.0~~ ≥ **85.0** percent to ~~125.0~~ ≤ **115.** percent of the target strength or, ***failing that***, not more than 1 in 200 tested are outside of 85.0 percent to 115. %, and none are outside of the relative range of 80.0 % to 120 % of the target strength. • The results meet the batch acceptance criteria for your established AQL level when the results are evaluated against the 'process variability unknown—standard deviation' criteria for 'normal inspection' in ISO 3951 (or ANSI Z1.9, its American equivalent). If your test results meet all of these criteria, ~~they are~~ the active results can be classified as *readily* ~~*pass*~~ passing and, provided you have adequate controls on all of the physical properties of the components in your formulation, all of the data for the development and the other initial conformance batches supports the batch-to-batch reproducibility of the results obtained, you ~~can~~ may be able to start routine batch testing using the Standard ~~Verification~~ Classification Method (SC~~V~~M) described in section VII. If your test results fail to meet any of these criteria, we recommend that you test an additional set of samples and compare the results found for the combined sets with the *marginally* ~~*pass*~~ passing criteria described below." [**Note:** The importance of meeting the "85 % to 115 % of target" range cannot be over emphasized.]	(Continued) **For RSD:** For a batch to be characterized as "readily passing," all of the results found should be within the **USP**'s "any article" *expectation range* and not just its lifetime "none" range. This is the case because the batch percentage tested is typically less than 0.1%. Thus, almost all results must be inside of 85 % to 115 % of the permitted target because finding any outside of that range clearly establishes the reality that, post release, some sets of 30 may fail the **USP**'s "post release" content uniformity criteria by having more than 1(for "tablets") or 2 (for "capsules") outside the expected range, and, if such 30's are tested, the batch will fail. **For Set Mean:** A critical CGMP-compliance issue (that the Draft seems to ignore) is whether or not the overall mean is sufficiently close to the target level to ensure that batch meets the CGMP formulation requirement set forth in **21 CFR 211.101(a)**. **For Sampling-Point Means:** As stated previously, the samples are from different time points not from different locations. Moreover, since the expectation for all individuals in small samples should be that they are mostly in the relative range from 92.5 % to 107.5 % (based on the RSD for this category), the means expectation range should be inside of the expected values range. Furthermore, the mathematical precision should be the same for both limits **For Individual Active's Results:** For a batch to be characterized as "readily passing," almost all of the results found must be within the **USP**'s "any article" *expectation range* and not its lifetime "no units can be outside of" range. This is the case because the tested % of the batch is typically less than 0.1%. In such cases, all results should be inside of 85 % to 115 % of the permitted target because finding any outside of that range clearly establishes the reality that, post release, some sets of 30 in the batch may fail the **USP**'s content uniformity criteria by having more than 1 (for "tablets" or 2 ("for capsules") outside the expectation range, and, should such 30's be tested, the batch will fail.

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
"289-291"	Change to "If your dosage unit test results fail to meet the criteria for the readily pass classification, compare the weight corrected test results to the following criteria:" This reviewer cannot support the commenter's suggestion because it conflicts with clear in-process CGMP material assessment requirements that require the ***characteristics*** of the material to be assessed, not some "*weight-variability corrected*" *characteristic* as the commenter is again proposing. Provided the Draft is revised to limit the scope to the content uniformity of the active, this reviewer suggests the following CGMP-compliant alternative: "If your dosage unit test results fail to meet the criteria for the r*eadily passing* classification, you should first investigate the findings to see if there are any processing factors associated with a given sampling point that may have cause the data at that point to one or more results that either caused the batch not to meet a given "readily passing" criterion. This is especially important in cases where the problem point or points are associated with "significant events," (like the start of dosage unit formation or the end of dosage-unit formation or an equipment-related interruption and restart), where the procedure may easily be changed (for example, changing the end of formation point from "after the last of the final blend has been loaded into the hopper, continue running until the level of blend in the hopper reaches the '25 %' full mark" to "after …into the hopper, continue running until the level … reaches the '50 %' full mark) to reduce the risk of an excursion. If any valid result is outside of the range from 75 % to 125 % of target, all that you should do is investigate and revert to the formulation development stage because the current process obviously does not reliably produce in-process units that meet the CGMP minimums. ***In some cases***, you may be able to justify evaluating ~~assay the remaining dosage units (all 7 units per location)~~ another set of dosage units and ~~compare~~ comparing the test results for the combined sets to the following criteria:"	To comply with Amended line 283, which describes how many to test. Plus, clarify the data are weight corrected for those not familiar with PQRI proposal. This reviewer already addressed this issue in his basis statements in Row IV - B "273" When one finds results outside of those expected, the first thing that they should do is review the results and look to see if the unexpected results have a possible cause that can be addressed by a change in procedure. For example, if the most of the results for "Point 22" are much different that the results found for "Point 21" or "Point 23" and "Point 22" corresponds to a "significant event" such as "restart after tooling change" look to see what can be done to change the restart procedure and/or the point at which formed dosage units are again collected as part of the batch that could reduce the risk of including such "different" units into the batch of dosage units suitable for further processing. However, unlike the **USP**'s "grab sample" approach (directly applicable **only** to "in commerce" drug product) where one can justify the relaxation of the acceptance criteria for sample average properties like the mean and the RSD when the testing is expanded from one level of units to a larger number of units, sampling that complies with the CGMP should yield results that give "mean" and "RSD" values that are respectively: a. Closer to the target level and b. Smaller or certainly not larger than the value found for the smaller number of ***batch-representative*** samples tested. Thus, to even propose to widen the RSD for acceptability, those that wrote the Draft are "admitting" that the sampling and testing plans they propose do not reflect the CGMP minimum requirement that both must be *representative of the batch*. Moreover, during criteria verification it is important to increase testing whenever the initial testing results do not meet the *scientifically sound sample specifications* and *batch acceptance criteria*.

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
337	In addition to the amendment text, add another bullet: • Previous routine test was per SCM and passed SCM criteria. This reviewer cannot agree with the commenter's suggestion because it is a needed but incomplete change – much more is needed. Provided the guidance is corrected to conform with all of the clear requirement ***minimums*** of the applicable CGMP regulations, the sample number minimums are corrected to "50 batch-representative dosage units" for 'SCM' and "200 batch-representative dosage units" for 'MCM,' and the statistically flawed switching rule for switching from 'SCM' to 'MCM' based on a single excursion are corrected, this reviewer does supports changing the switching rules as follows: "Use 'SCM' criteria your basis Inspection Plan when: 1. The initial process conformance batches have established that, under certain conditions, a "reduced" inspection plan can be used. 2. Production is at a steady rate. 3. Your initial, post-conformance studies have produced more than 10 consecutive batches that met the 'MCM' criteria and you are authorized to switch to an 'SCM' plan. 4. The routine test for the previous batch was 'SCM' and passed 'SCM' criteria. 5. Your current campaign consists of at least 10 consecutive batches and the routine test for the previous 5 batches was 'MCM,' but each batch met the 'SCM' criteria."	3 scenarios to use SCM exist in PQRI document: 1. Validation was readily pass and we are just starting production 2. Routine test method is SCM and we continue this as long as we keep passing. 3. Routine method is MCM, but switching rule is met. This draft and the commenter seem to have recognized this when they require not less than 5 consecutive batches that are tested using a "full" set but pass the "reduced" set criteria before switching from 'MCM' to 'SCM.' However, the proposed rule for 'SCM' to 'MCM' has no such valid provision. Furthermore, before a "reduced" inspection plan (the 'SCM' plan here) can validly be considered for implementation, the valid use of any "switching rules" in inspection requires (based on the controlling guidance provided in applicable recognized consensus standards, ANSI Z1.9 (and ISO 3951): 1. Production to be at a steady rate, and 2. Initially, at least 10 batches have been inspected using the normal inspection plan (the 'MCM' plan here) without any being rejected. Thus, unless the production process: a) continually produces batches without interruption, or, when production is intermittent, b) produces more than ten (10) batches in each campaign the use of any reduced ('SCM') inspection is, at best, difficult to justify. Yet, this reviewer notes that this guidance failed to mention much less address the preceding realities. Finally, for those who claim that testing "200" is onerous in batches upwards of 250,000 in size should note that the number in question is less than 0.1 %! (1 in a 1000) of the units in the batch for such batches and less than 0.01 % (1 in 10,000) for batches larger than 2,000,000 dosage unit (a "batch size" that is becoming increasingly common today – a size that should soon trigger a revision to said consensus standards since their current tables end with sizes of 150,001 to 500,000 and 500,001 and over, the table needs at least one (1) more level (probably at 2,000,000 as follows: Replace: "500,001 and over" with: "500,001 to 2, 000,000," and Add: "2,000,001 and over."

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
382	In addition to the amendment text, add another bullet: • Previous routine test was per MCM and passed MCM criteria This reviewer cannot agree with commenter's suggestion here because, as stated for the 'SCM' case, it is insufficient. Provided the same caveats that are stated for the case for the 'SCM' criteria are accepted here was, this reviewer proposes the following 'MCM' criteria: "Use 'MCM' criteria as your basis Inspection Plan when: 1. The initial process conformance batches have established that a 'NORMAL' inspection plan should be used. 2. You are just starting production and have not yet produced more than 10 consecutive batches that met the 'MCM' criteria. 3. You do not produce more than 10 batches in any run or campaign. 4. Routine testing for the previous batch was 'MCM,' or 5. Routine test for the previous batch was started under 'reduced' inspection ('SCM'), but had to be inspected under a "normal" inspection plan ('MCM') or an augmented inspection plan (not provided in this guidance) and this is the third such occurrence in the last 5 consecutive acceptable batches. 6. The previous batch was rejected. 7. The previous five (5) batches were inspected under an 'augmented' sampling plan (not provided) and met the 'MCM' criteria."	3 scenarios to use SCM exist in PQRI document: 1. validation was marginally pass and we are just starting production 2. routine test method is MCM and we continue this until we can switch. 3. last batch started as SCM, but had to go to MCM pass The basis for this set of 'MCM' criteria is stated in the previous section on the 'SCM' criteria.

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
Amendment line number 395 (new text)	Minor changes to last sentence: "That is, to establish justified assignable cause(s), take necessary corrective actions, and if appropriate, repeat the powder mix assessment, stratified sample correlation, and initial criteria establishment procedures." This reviewer cannot and does not support the changes proposed here. However, this reviewer does agree that the text needs to be improved and suggests the following: "When a batch fails, *in addition to starting an investigation into that batch's failure*, the firm must also investigate all associated batches, released or not." Moreover, any *scientifically sound* CGMP-compliant inspection plans (the CGMP's *sampling plans* and *test procedures*) must include a switch to more intensive inspection whenever there is a real failure of a batch and, when unexpected results are obtained, also switch to more intensive inspection whenever this unusual pattern occurs. [**Note:** The consensus standards (ANSI Z1.9 and ISO 3951) provide a simplified discussion of this in subsection entitled "**NORMAL, TIGHTENED, AND REDUCED INSPECTION**."]	If a single lot fails SCM and MCM, and the root cause is identified to be due to a deviation from the validated process (say materials were not added in correct order), we do not want to have to go through revalidation of all the correlations, just reject the lot and put measures in place to prevent recurrence. But, if the process is 'broken' and must be fixed, then this all needs to be done Since validation is an ongoing, a failure cannot require a "revalidation." Moreover, the commenter has deliberately mischaracterized the proposed changes, as minor changes, when, in fact, *as the commenter's rationale clearly reveals*, the commenter knows that the proposed changes are major changes. However, *under the law*, the test must be changed to conform to the applicable CGMP minimums. Since this Draft is a guidance document, it compels nothing. Moreover, under CGMP, the judgment permitted to the manufacturer is exactly how to meet the clear requirement *minimums* stated in the regulations – ***compliance is required*** and ***knowing non-compliance subjects those who do to the risk of prosecution under the appropriate statutes as well as renders any batches produced in a non-complying manner adulterated***. [**Note:** Based on the commenter's remarks, the commenter is either unaware of the regulations and thus unqualified under CGMP (**21 CFR 211.25**) or supporting the knowing non-compliance with the CGMP and, if this is the case, conspiring to subvert the regulatory process.]
416	(CCTD17 3.2P.3.3). Replace with P.3.4 This reviewer leaves this issue up to Agency to resolve.	Drug Product Draft Guidance January 2003 lists controls for critical steps under P.3.4
429	(CTD 3.2.P.4.1) Replace P.5.1 This reviewer leaves this issue up to Agency to resolve.	P.5.1 applies to specifications for drug products
436	(CTD 3.2.P.2.2) Replace with P.2.3 This reviewer leaves this issue up to Agency to resolve.	P.2.3 applies to manufacturing process development.

Line #	Comment/Recommendation for Revision / Observation	Comments regarding test / Basis
Revised Attachment 1 flowchart, line 498	Move box "Assay at least 7 dosage units per each location, weight correct each result" (from line 507) immediately after box that says "Assay 2nd and 3rd blend samples from each location. This reviewer does not support the text in the boxes or the change in placement proposed. *Scientifically sound sampling plans* and *test procedures* (inspection plans) for non-discrete materials ("blends") include sufficient multiple-aliquot assessments of sample uniformity so that the testing, within-sample, between-location and error variance components can be properly assessed without the need to perform any additional testing – hopefully, the commenter is not, *as the commenter seems to be*, advocating the use of less-than-sound inspection practices?	The dosage unit data is generally used as part of the investigation to help correlate blender problems or identify sample bias. As has been clearly established by this reviewer: **1.** Sampling plans proposed for the blend sampling do not conform to the *scientifically sound* and *appropriate requirements* of either **a)** the CGMP regulations or, for that matter, **b)** inspection and analytical science **2.** Active uniformity cannot be validly used to establish what is required, material uniformity for all critical variable factors including, but most certainly not limited to, the active(s) in the material being assessed. **3.** The CGMP regulations clearly require the assessment of the uniformity of the characteristics, not the *biased weight-corrected characteristic* proposed here.
Revised Attachment 1 flowchart, line 508	Replace box that says "Assay at least 7 dosage units per each location, weight correct each result" with a box that says "Use dosage units to verify adequacy of powder mix." This reviewer rejects the commenter's proposal along with the original text because the in-process dosage units collected as the Draft suggests cannot be validly used to demonstrate the uniformity of the mix because there is no way to ensure that the dosage-unit samples are from the locations where the alleged blend sample error occurred and the active level is but one, *and not the most critical one in many instances*, of the critical variable factors whose uniformity must be properly assessed in *each batch* (**USA v. Barr Laboratories, Inc., et al.**, Civil Action No. 92-1744, (**812 Federal Supplement 458 (DNJ) 1993**, "Barr Opinion") to establish the uniformity of an in-process drug-product material mix.	Although the results were assayed earlier to help in the blend investigation, now we have identified blend sample error so they must be used to demonstrate uniformity of mix. Factually, because there are steps between the blend sampling and the generation of the dosage units, other than weight, that contribute to the variability in the values observed in the dosage units, the level of active in the dosage units is, at best, a biased estimate of the uniformity of the active in the mix but, because it fails to assess the levels of the other critical components in the formulation cannot validly be used to verify the "adequacy of powder mix." If your manufacturing system includes sampling plans that generate "sample error" or "sample bias" of the type described, then your system does not comply with CGMP and the drug products produced by such systems are adulterated and cannot, therefore, be legally offered for sale. Moreover, manufacturers have an absolute legal duty to comply with any clear regulation that the Agency may not legally contravene by publishing a nonconforming guidance document (**Berkovitz v. US, Supreme Court 1988, 486 US 531, 100 L Ed 2d 531, 108 S Ct 1954**).

"Attachment 2
'PhRMA Comments"

Section G-Line	Comment / Observation	Rationale / Basis
I 18-23	Include in the introduction that the guidance allows the manufacturer to assess the adequacy of the powder mix/drug uniformity by the use of stratified in-process samples instead of continuing to struggle with blend sampling issues, provided that a feasibility assessment is made prior to implementation of the stratified sampling approach. This reviewer cannot support the commenter's suggestion because the commenter's "guidance allows the manufacturer to assess the adequacy of the powder mix/drug uniformity by the use of stratified in-process samples instead of continuing to struggle with blend sampling issues " does not meet the applicable clear CGMP requirements for in-process materials that require the assessment of uniformity at each significant phase during manufacturing (**21 CFR 211.110**). In addition, the alternate approach proposed does not assess the "adequacy of mixing" – at best the alternate approach provides a non-representative sample estimate of the uniformity of the active and not, *as required by the in-process CGMP regulations for drug products*, a *batch-representative* assessment of the overall uniformity of the final blend (which this guidance persists in calling the blend though there are other pre-final-blend processing steps that, *as the recent Pfizer article clearly shows*, need to have their uniformity assured and appropriately controlled). Hopefully, the Agency will read and heed this reviewer's statements and revise this draft guidance in a manner that conforms with the clear requirements of the CGMP regulations that apply to in-process materials and in-process drug products.	The key advantage of the guidance should be stated in the beginning of the document. The applicable CGMP regulation ***minimums*** governing in-process materials and the drug product clearly require a firm to assure the uniformity and integrity of each batch of drug product and clearly specify that such assurance shall include the monitoring the output and validating "the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product." (**21 CFR 211.110(a)**). In addition, **21 CFR 211.160(b)(2)** requires all in-process samples to be *representative* (as that term is defined in **21 CFR 210.3(b)(21)**), but the "stratified sampling" procedure proposed in the Draft, at best, does not ensure that the samples taken are *batch representative* samples nor, for that matter, does it sample sufficient samples for the assessment of all critical variable factors – not just *active uniformity* – that, *under* ***21 CFR 211.110***, must be assured. In addition, **21 CFR 211.110(c)** states (emphases added), "**In-process materials shall be tested** for identity, strength, quality, and purity as appropriate, **and approved or rejected by the quality control unit, during the production process**, e.g., **at** commencement or **completion of significant phases** or after storage for long periods." Clearly, **21 CFR 211.110(c)** requires the **final blend** of *each batch* to be tested and released or rejected by the firm's quality control unit before it can be processed into dosage units. Finally, in 1988, the United States Supreme Court unanimously ruled that an FDA official cannot legally issue *any document* that does not conform to any clear regulation. **Thus, the 1988 Supreme Court held that the FDA's issuing guidance that does not conform to the clear requirements of the CGMP regulations is a violation of the law.**

Section G-Line	Comment / Observation	Rationale / Basis
III 82-83	Change text to "Compare the stratified in-process dosage unit data with the finished dosage unit data to determine whether in-process samples may be used to assess the uniformity of content." Provided, **a)** this draft guidance is retitled and the text modified so that both unmistakably limit the guidance provided to assessing only one facet of the uniformity of the batch, active uniformity, and **b)** the non-representative by definition "stratified sampling" is replaced with *batch-representative* dynamic sampling defined using good inspection science in a CGMP-compliant manner, this reviewer would suggest the following language be used: "Compare **the results obtained and their batch implications from the evaluation of an appropriate number of batch-representative dynamically sampled** ~~stratified~~ in-process dosage units ~~data~~ with the **corresponding data from the testing of a similarly appropriate number of batch-representative** finished dosage units ~~data~~ to determine **whether or not** in-process samples may be used to assess the **drug product batch's** uniformity of content (for each active ingredient)."	Clarity Adherence to the precepts of sound inspection science and conformance to the clear applicable requirement ***minimums*** in the CGMP regulations. The phrase "uniformity of content" is also applicable to ingredients other than the active and the text should limit said phrase to the active unless it is evident to all that the guidance is restricted to assessing only the uniformity and integrity of the active(s) in the drug product. Until the guidance is retitled and rescoped to explicitly limit the guidance to ONLY the uniformity of the active or actives in any aspect of the manufacture of the drug product, this reviewer must suggest that the parenthetical phrase, "(for each active ingredient)", be included in the text.
IV. A. 128	How does the agency expect us to determine sampling errors? Please specify. This is a question that the industry and not the Agency should be able to answer. Moreover, if a manufacturer cannot provide the *scientifically sound* approach they use to the Agency, this reviewer recommends that said firms be barred from submitting any new applications until they are able to provide this information. Finally, the question that the commenter should be answering is "how do we ensure that the risk of sampling errors is minimized?"	Not explained. As a scientist, this reviewer knows of several valid approaches that can be used, but thinks that this is an area where the CGMP-compliant industry should have developed a *scientifically sound* approach that they use during formulation development to ensure that their formulations are highly uniform, mechanically stable, and properly sampled.

Section G-Line	Comment / Observation	Rationale / Basis
VI.D. 308-315	Move Sub-section VI.D to Section VII. This reviewer does not support the commenter's suggestion to move this Subsection because its placement is logically correct. However, because the section covers more than just deciding "sampling locations," this reviewer recommends that this Subsection be re-titled and revised as follows: " **D. Summary of Findings and Setting the Inspection Plan For Routine Manufacturing** 1. Findings Summary We recommend that you prepare a *scientifically sound and justified* summary of ~~the~~ your in-process data analysis from the powder mix assessment and ~~stratified~~ dynamically sampled, batch-representative formed-dosage-unit sample testing studies that you have performed. 2. Routine Manufacturing Inspection a. The Final Blend From the blend analysis for all conformance batches, establish the minimum set of sampling locations (typically, about 5 for sampling from the blend's container and 'n+2' when sampling from an ordered set of 'n' drums) that, on average, give the same uniformity picture as the full sets sampled. Set your inspection plan to take duplicate multi-dose samples from the furthest apart locations and the mid-point location, and singlicate multiple-dose samples from the remaining sampling locations to provide some estimates of within-location sampling variability (about 8 test aliquots for the container samples and about 'n+5' for the containers. Make the acceptance criteria and post-acceptance decision criteria as follows: 1) If blend samples tested meet all blend acceptance criteria, set the routine dosage-unit testing to start at **Stage 1**. 2) If the blend samples tested meet the range criterion but not the other criteria, set the routine dosage-unit testing to start at **Stage 2**. 3) If the blend samples do not meet the range criteria but are all in the range of from 87.0 % to 113. %, set the routine dosage-unit testing to start at **Stage 3** 4) If any of the blend samples' results are outside of the range in **Step** '3),' refer the Batch to the QCU and proceed as they direct. (Continued on next page)	More appropriate to be under ROUTINE MANUFACTURING… rather than under VERIFICATION OF MANUFACTURING CRITERIA Subsection VI.D addresses much more than assigning sample locations for the blends and sampling points for the formed dosage units and is properly placed. All that needs to be corrected is its title and, in some areas, its language. Those who drafted this portion of the guidance seem to be attempting to turn a CGMP requirement (**21 CFR 211.160(b)(2)**) that the in-process sampling be *representative* of the batch into an explicit guidance "suggestion" that choosing a number of points "to represent" the batch somehow satisfies this CGMP requirement when it does not *per se* do so. The reality is that this juxtaposition of terms, "to represent the entire routine manufacturing" for the clear regulatory requirement of **21 CFR 211.160(b)(2)**, "Such samples shall be representative and properly identified," is neither *scientifically sound* nor CGMP-compliant. This is the case because the samples from any set of locations or points, including those from sets that are not *batch representative*, can be validly held "to represent" the properties of the batch. However, only those samples from point or location sets that meet the requirements for a dynamically sampled *batch-representative* set can satisfy the CGMP requirements set forth in **21 CFR 211.160(b)(2)**. Thus, the guidance should specifically require the "point set" selection to include the start point (just after the manufacturer begins to collect the formed units as a part of the batch) and the end point (the last units included in the batch) because, for a *dynamically sampled sample,* the set must span the batch to be "*batch representative*", as required by the CGMP regulations. Similarly, *for static sampling*, a *batch-representative* "location set" must be inspected (sampled and tested) and the sampling plan used must be proven to be an unbiased set of multiple-dose samples that are sufficient in amount (for blends) or number (for dosage units) to provide more than enough sample for all possible testing, and, where indicated, a reserve sample. (Continued on the next page)

Section G-Line	Comment / Observation	Rationale / Basis
VI.D. 308-315 (Continued)	(Continued) b. The In-Process Dosage Units 1) From the data analysis, you should establish the ~~stratified~~ dynamically formed dosage-units' sample locations for routine manufacturing, taking into account significant process events and their effect on in-process dosage unit and finished dosage unit quality attributes. 2) You should identify *and designate* ~~at least 10~~ not less than 10 "routine production" sampling ~~locations~~ time points (the start point, the end point, and not less than 8 approximately evenly spaced intermediate points) during capsule filling or tablet compression ~~to represent~~ that your studies have established to be approximately as representative of the entire routine manufacturing of the formed units that comprise the batch as the entire set while making provision for the inclusion of any 'significant events' that may occur during this production step. 3) In addition, the number sampled at each point should be appropriately adjusted to be that integer multiple of all of the dosage forming stations in the forming system that is required to satisfy all of the firm's pre-established sampling and sample evaluation (examination and testing) for the said formed units. 4) You should use the outcomes from the blend testing to guide you as to the number of representative samples that you need to select for analysis from the full set sampled at each location (for example, *if you have 10 sampling points*, 5 at random for **Stage** 1 [50], 20 for **Stage 2** [200] and 40 for Stage 3 [400]. [**Note:** You should continue to use the outcomes observed to refine your decision making and physical material controls within the AR and CBE-0 flexibility permitted by the Agency. When you have accumulated a sufficient history of continuously passing batches at both the blend and the formed-dosage material and the data clearly support that your production batches are all consistently close to their targets, you may be able to establish and justify switching to a set of inspection plans would permit you to use the applicable ISO (ANSI) 'process variability known' ('PVK') plans as their basis to further reduce the drug-product "starting point test sample numbers" while still preserving the ability to use the existing plans should the results indicate that such a step is required. These 'PVK'-based plans would, contingent upon the AQL level appropriate to your product (0.10 to 1.5 % nonconforming), allow you to have a Stage A ('REDUCED' inspection) plan that need only test 12 to 22 units, and a Stage B ('NORMAL' inspection) plan that need only test 42 to 71 units coupled with the permissible (Continued on next page)	(Continued) Therefore, this commenter has altered the Draft text to reflect the preceding factual scientific and regulatory realities.

Section G-Line	Comment / Observation	Rationale / Basis
VI.D. 308-315 (Continued)	(**Note** continued) option to switch to the 'process variability unknown' ('PVU') case plans at Stage 2 and proceeding from there as the 'PVU' set guides you. Thus, those who develop truly uniform robust blends may be able to justify inspection plans that have a *scientifically sound* "REDUCED" testing level that establishes the validity of testing *as few as* 8 (blend vessel) to about 15 (blend-IBCs) *batch-representative* blend samples and 12 (or, if your firm is "6 sigma" quality oriented, 17) *batch-representative* dosage-unit samples when your history truly supports a 0.1 % AQL.]"	
VII. A.2. 348	Add a footnote as follow: (3) weight correct[17] [17] Allow for the option of not weight correcting the stratified unit dose data during routine batch manufacture. The Draft's proposal is at odds with the clear in-process CGMP requirement "to validate" the uniformity of each characteristic, in this instance, the "active level," in the dosage units (and not some adjusted characteristic as the commenter proposes here). No footnote should be added; instead, the Draft's "(3) weight correct" should either be removed or restated as "(3) weight correct ONLY for the purposes of comparing the distribution of the weight-corrected dosage-unit data to the distribution of the blend data,"	Using non-weight corrected data to pass routine manufacturing criteria is more stringent, but it allows for only one set of calculations to pass both routine criteria and the content uniformity test Factually, to meet the clear in-process CGMP "characteristics" monitoring requirements **of 21 CFR 211.110(a)**, the "as is" active level data must be used to determine the uniformity of the batch of dosage units with respect to its active level. Clearly, the text here does not conform the clear requirements of the applicable regulation here and, because the FDA's guidance is required by law to conform to clear regulations, the draft needs to be appropriately corrected.
VIII 415	We suggest revising this sentence to read: "We recommend that you provide the following information, if available, in the … ." *While this reviewer agrees that the information from the initial full-scale conformance batches produced for the initial process "Performance Qualification" confirmation of process reproducibility may not be available*, to submit an application, the manufacturer is supposed to have fully developed their drug product processes, including production of at least one (1) process conformance demonstration batch, and, thus, all the information needed should be available before a submission is filed. Therefore, this reviewer cannot, in good conscience, agree with the commenter's suggestion here unless the commenter's intention is to admit that the commenter submits processes that they do not know are valid and well-controlled for FDA review and approval with: **a)** the hope that, *after approval*, the production process may consistently produce acceptable batches that meet the CGMP ***minimums*** **and b)** the knowledge that their hope may not be realizable – an apparently clear subversion of the regulatory process.	Most valuable data would be generated from validation batches which most likely are not made at the time of filing. If the commenter truly believes that the "Most valuable data" required to establish the validity of their processes is obtained from their "validation batches" but, though the commenter knew the firm needed this, currently unavailable, "Most valuable data," the commenter is submitting filings lacking this information because the Agency's policy is that such can be made after approval. Given the commenter's position and the commenter's knowledge of what is needed, it would seem that the Agency should strongly consider revisiting that policy. If needed data is not available, the firms should withhold their filings until such time as the requisite data, including that data required to assess the uniformity of all critical variable factors, including, but most certainly not limited to, active level, is available.

Section G-Line	Comment / Observation	Rationale / Basis
VIII 416,429,436	Please consider consolidating all information provided into *single* CTD section, preferably CTD 3.2.P.3.3. This reviewer does not agree with this recommendation because the guidance should place it where the CTD specifies that it be placed. Moreover, the commenter's remarks ignore several realities. First, this reviewer does agree with the commenter that the law in the United States, as interpreted by the regulations and binding FDA policies does require this to information to be available and, in this case, filed for any drug product approved by the US FDA. However, other governments use the US regulations, final Agency guidances, and Agency policies as the basis for their regulations, guidances, and policies. Finally, today's computerized systems make it child's play to "compile, link, and review" the same information into a variety of formats. If other countries using the CTD format do not currently require that the uniformity of their drug products be established in their submissions, they should do so or the Agency should not enter into an MRA with that government's corresponding agency.	Information is spread over different sections of each application, making it difficult to compile, link, and review. Under the MRA (**21 CFR 26**), the regulatory control systems used by the US and an covered government that wishes to use the MRA process must have *equivalent systems* and, if the commenter's remarks are true, then none of the candidate EU countries should be considered for an *equivalence system* until that country's government has established that their firms require all drug product processes to produce drug products that are uniform with respect to all of their critical variable factors at every stage in their manufacture. This document is an example of the ease with which information can be compiled, linked and reviewed even though the reviewer's remarks are spread much more widely (across multiple sections [one for each commenter] each in its own format and with certain topics discussed in different parts of each sections) than in three (3), well-defined sections of a "CTD."
General Comments on multilayer tablets	Indicate how the guidance is to be applied to multilayer tablets where the actives are in different layers. Indicate how to evaluate stratified samples of bilayer tablets. Since the commenter clearly recognizes that the published Draft cannot be used to address drug products that are multiple-layer dosage units, the Agency can either restrict the guidance's Scope to "single-layer dosage units or, *if it wishes to address both single- and multiple- layer dosage units*, adopt the approaches recommended by this reviewer in this review or those contained in the "revised Draft" he submitted to this docket that was posted to the FDA Public Docket 2003D-0493 on 30 January 2004. Since the CGMP regulations that apply to the in-process materials and drug products (as the title of **21 CFR 211.110**, "Sampling and testing of in-process materials and drug products," clearly states) and said regulations clearly require the assessment of the uniformity of the drug product produced at each significant manufacturing phase, it should be clear that the uniformity of each blend must be assessed for all critical variable factors. **Hopefully, the Agency will revise this guidance for the *uniformity of the active* in** (continued ➔)	If there are two different assays for the two different actives, one could be in a situation of having to apply SCM for one active and MCM for the other. First, this reviewer notes that the rationale here has nothing to do with bilayer tablets *per se* as it addresses the reality that dosage units containing more than one active that cannot be evaluated using the same test procedure may have the outcome indicated by the commenter even when said actives are present in a single-layer dosage unit. The acceptance criteria are based on weight corrected data; the guidance should also provide for use of non-weight corrected data. As this reviewer has previously established the use of weight-corrected active values to meet the in-process CGMP requirement ***minimums*** is a non-conforming choice that must not be used if you wish to comply with the clear regulations governing their firms' conduct. --- ***in-process materials and drug products* that are *tablets* and *capsules* so that it at least conforms to CGMP regulations' clear requirements with respect to assessing the *uniformity of each active*.**

Section G-Line	Comment / Observation	Rationale / Basis
Attachment II Revised Attachment 2 flowchart	The 4 boxes at the top of the flowchart are confusing to some. We recommend listing 3 situations that allow one to test SCM and 3 that allow MCM in a bullet list above the flow chart. Begin the flowchart with the first diamond. Use SCM routine criteria if: 1. validation was readily pass and you are just starting production, or 2. routine test for the previous batch was SCM and passed SCM criteria, or 3. routine test for the previous batch was MCM, but switching rule is met Use MCM criteria if: 1. validation was marginally pass and you are just starting production, or 2. routine test for the previous batch was MCM, or 3. routine test for the previous batch started as SCM, but had to go to MCM to pass Provided the guidance is corrected to conform with all of the clear requirement ***minimums*** of the applicable CGMP regulations, the sample number minimums are corrected to "50 batch-representative dosage units" for "SCM" and "200 batch-representative dosage units" for "MCM," and the statistically flawed switching rule for switching from "SCM" to "MCM" based on a single excursion are corrected, this reviewer does not object to the modified form of a "flow diagram." However, if the commenter insists on making these "flowcharts," the commenter should revise this suggestion to conform to the well-understood rules governing flowcharting. Finally, based on this reviewer's observation and basis statements, this reviewer would recommend substituting the following text for the commenter's suggested text: "Use 'MCM' criteria as your basis Inspection Plan when: 1. The initial process conformance batches have established that a "normal" inspection plan should be used. 2. You are just starting production and have not yet produced more than 10 consecutive batches that met the MCM criteria. 3. You do not produce more than 9 batches in any run or campaign. 4. Routine testing for the previous batch was MCM. 5. Routine test for the previous batch was started under "reduced" inspection ("SCM"), but had to be inspected under a "normal" inspection plan ("MCM") or an augmented inspection plan (not provided in this guidance) and this is the third such occurrence in the last 5 consecutive acceptable batches. 6. The previous batch was rejected. 7. The previous five (5) batches were inspected under an "augmented" sampling plan (not provided) and met the "MCM" criteria (Continued on next page).	clarity Though the attachments provided do not adhere to them, there are well-understood rules that govern the construction of flow charts that the commenter should adhere if the commenter insists on casting these as "flowcharts." In the testing of a small number of samples from a large population, statistics-based decision rules (as these purport to be) should provide for variation in outcomes that must be ignored until a sufficient number have occurred to indicate that an action is needed. This draft and the commenter seem to have recognized this when they require not less than 5 consecutive batches that are tested using a "full" set but pass the "reduced" set criteria before switching from "MCM" to "SCM." However, the proposed rule for "SCM" to "MCM" has no such comparable provision. Furthermore, before a "reduced" inspection plan (the "SCM" plan here) can validly be considered for implementation, the valid use of any "switching rules" in inspection requires (based on the controlling guidance provided in applicable recognized consensus standards, ANSI Z1.9 (and ISO 3951): 1. Production to be at a steady rate, and 2. Initially, at least 10 batches have been inspected using the normal inspection plan (the "MCM" plan here) without any being rejected. Thus, unless the production process: • continually produces batches without interruption, or, when production is intermittent, • produces more than ten (10) batches in each campaign the use of any reduced ("SCM") inspection is, at best, difficult to justify. Yet, this reviewer notes that this guidance failed to mention, much less address, the preceding realities. Finally, for those who claim that testing "200" is onerous in batches upwards of 250,000 in size should note that the number in question is less than 0.1 %! (1 in a 1000) of the units in the batch for such batches and less than 0.01 % (1 in 10,000) for batches larger than 2,000,000 dosage unit (a "batch size" that is becoming increasingly common today – a size that should soon trigger a revision to the recognized consensus standards since their current tables (Continued on next page)

Section G-Line	Comment / Observation	Rationale / Basis
	(Continued) Use "SCM" criteria your basis Inspection Plan when: 1. The initial process conformance batches have established that, under certain conditions, a "REDUCED" inspection plan can be used. 2. Production is at a steady rate. 3. Your initial, post-conformance studies have produced more than 10 consecutive batches that met the MCM criteria and you are authorized to switch to an "SCM" plan. 4. The routine test for the previous batch was "SCM" and passed "SCM" criteria. 5. Your current campaign consists of at least 10 consecutive batches and the routine test for the previous 5 batches was "MCM," but each batch met the "SCM" criteria	(Continued) end with sizes of 150,001 to 500,000 and 500,001 and over, the table needs at least one (1) additional level (probably at 2,000,000 as follows: Replace: "500,001 and over" with: "500,001 to 2, 000,000," and Add: "2,000,001 and over."

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

C-11 Upsher Smith Laboratories, Inc., Posted 1 April 2004

The Upsher-Smith comments begins by stating:

"Upon review of the Draft Guidance on the Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessments, Upsher Smith Laboratories, Inc. (USL) would like to submit several comments and suggestions for your consideration. Although we applaud the movement toward a more scientific and/or statistical approach to blend assessment, the proposed draft guidance appears lacking in an understanding of the difficulty to apply the proposed rules to a manufacturing and testing organization."

> While this reviewer understands the commenter's remarks, this reviewer can only trust that the *scientifically sound* and CGMP-conforming responses he gives to the commenter's issues will help the commenter find a CGMP-compliant operational protocol for the manufacture of the drug products that they are currently making or intend to make in the future.

Upsher-Smith's reviewed comments …

"1. In the guidance, there is no mention of the USP requirements on the Uniformity of Dosage Units <905>, in which Weight Variation may be used in some cases. If a product contains 50 mg or more of an active ingredient comprising 50% or more, by weight, of the dosage unit, special consideration could be made and the products in this category excluded from this guidance. At a minimum, criteria could be established during development and validation work through the recommended correlation of in-process stratified sampling with powder mix and finished product. Would it be possible to incorporate the Weight Variation instead of the Standard Criteria Method (SCM) and Marginal Criteria Method (MCM) testing for routine testing based on the amount of active ingredient of the dosage unit?

> First, this reviewer notes that in **21 CFR 211.110(a)**, *for the tablet and capsule drug products this Draft emphasizes*, "Such control procedures shall include, but are not limited to, the following, where appropriate: (1) Tablet or capsule weight variation; (2) Disintegration time; (3) Adequacy of mixing to assure uniformity and homogeneity; (4) Dissolution time and rate; …" where, *in addition to addressing active uniformity*, weight, disintegration, dissolution time and rate, and other variable factors must be appropriately addressed for the final blends, formed dosage units and/or the finished dosage units.
>
> Thus, from this portion of **21 CFR 211.110(a)**, it is clear that "Weight Variation is an <u>additional</u> uniformity requirement that <u>must</u> be assessed in addition to the uniformity of the active in the final blend and the dosage units.
>
> Further, contrary to the commenter's statement, "USP requirements on the Uniformity of Dosage Units <905>, in which Weight Variation may be used in some cases," **none** of the **USP**'s *post-release* uniformity requirement specifications are <u>directly</u> applicable to the *pre-release* or *release* active uniformity requirements established **in 21 CFR 211.110**, **21 CFR 211.160**, **21 CFR 211.165**, **21 CFR 211.166**, or **21 CFR 211.167** as they apply to in-process materials, including the in-process formed dosage units, and the drug product <u>prior</u> to the release of the *batch* into commerce.

This is the case because the CGMP regulations ***require:*** **a)** specifications *appropriate to* a ***representative sample*** *of* the *batch* **and b)** the testing of a ***representative sample*** from the *batch* – the **USP**'s post-release uniformity specifications apply to the **USP *article***, a grab sample, and, as the **USP** states, the **USP**'s sampling plans are not statistical sampling plans and they do not even require the ***article*** sampled and tested to be ***representative*** of the part of the *batch* from which they were taken, much less, the entire *batch*.

In addition, the CGMP regulation ***minimums*** set forth in **21 CFR 211.110** are the controlling requirements and, as written, apply to the manufacture and release of each batch of ***all*** drug products.

As far as this reviewer can ascertain, there is no part of the CGMP regulations that excludes any drug product from any of the applicable in-process requirements set forth in **21 CFR 211**.

Worse still, there is no sound science that would support not assuring that such drug products are adequately uniform before they are released *because there will be no post-release evaluations* – don't assure uniformity because the post-release **USP** requirements do not check for active uniformity – an approach that is not only anti-quality and illegal but also ignores the need for the assessment of the uniformity of each "mix" for *other critical variable factors*.

In that regard, this reviewer further notes that the applicable "**WEIGHT VARIATION**" subsections, "UNCOATED AND FILM-COATED TABLETS," and "HARD CAPSULES," end the same way, "**assuming homogeneous distribution of the active ingredient.**"

Since, *after batch release*, *the **USP** permits homogeneity to be assumed*, it is even more important that the pre-release and release testing establish that the **USP**'s post-release assumption condition is met than when the **USP**'s post-release testing requires a "content uniformity" determination.

Finally, in 1998, the US Supreme Court (in *Berkovitz v. USA*) held that the Agency has no latitude with respect to issuing any written statement which conflicts with the ***clear*** requirements of any binding CGMP regulation.

Thus, the course of action being suggested is for the Agency to issue guidance that clearly conflicts with the legally binding, in-process, requirement ***minimums*** for the assessment of the uniformity of each batch.

To its credit, the Agency has apparently recognized that to do so would be to publish written guidance that plainly conflicts with one or more of the clear binding CGMP regulations for drug products – an activity that the US Supreme Court ruled was an illegal activity– and declined to follow the PQRI's non-conforming advice.

For all of the reasons cited, this reviewer recommends that Upsher Smith's remarks (concerning the in-process testing of blends and dosage units) be rejected by the Agency because they are clearly conflict with both sound inspection science and the law.

"2. During the verification of the Manufacturing Criteria (Section VI), there is a requirement to sample "at least 20 locations". This requirement does not seem to account for short tableting runs. For instance, if you were tableting for 10 hours...you would sample every 30 minutes, but if you were tableting for only one hour...you would be sampling every 3 minutes. For a short run, the 20 periodic locations do not seem to add any value to the data collected as you would anticipate very little difference between individual samples taken that closely together. Some consideration for the size of the run (either length of time or total number of tablets produced) would appear to be warranted to ensure appropriate statistical coverage."

This reviewer agrees with the commenter that some consideration for the size of the run should be given and would therefore again recommend that the coverage time points be expressed in terms of:

1. Level of non-uniformity observed for the final blend during the process development studies conducted to assess the uniformity of the final blend and
2. Approximate percentage of the batch allowed to be tableted between dosage-unit sampling points.

This reviewer's suggestion simply conforms to the dynamic inspection principle that inspection frequency should be inversely proportional to the expected level of non-uniformity.

In this instance, this reviewer suggests the following rules of thumb:

- If the *statistical estimate* of the *batch's* RSD, *at a confidence level of 95 % or higher*, for the final blend is "1.0 %" or less, then the sampling points can be spaced in a manner that permits up to 15 % of the batch to be formed into dosage units between sampling points.
- If the statistical estimate of the batch's RSD, *at a confidence level of 95 % or higher*, for the final blend is more than "1.0 %" but less than 2.0 %, then the sampling points can be spaced in a manner that permits up to 9 % of the batch to be formed into dosage units between sampling points.
- If the statistical estimate of the batch's RSD, *at a confidence level of 95 % or higher*, for the final blend is more than "2.0 %" but less than 3.3 %, then the sampling points can be spaced in a manner that permits up to 5 % of the batch to be formed into dosage units between sampling points.
- If the statistical estimate of the batch's RSD, *at a confidence level of 95 % or higher*, for the final blend is more than "3.3 %," then the final blend should not be formed into dosage units until the batch's statistically estimated RSD can be reduced to 3.3 % or less (this value is based on the PQRI's data mining' studies finding that there was only a valid correlation between the final blend RSD and the dosage unit's RSD when the final blend's observed RSD was 3 % or less [the 3.3 % limit chosen permits the observed samples' RSD to be a 10 % uncertain estimate of the batch's RSD at the final blend step]).

Hopefully, the preceding has addressed the commenter's concerns in a science-based manner without being overly prescriptive.

"3. Once we begin routine manufacturing batch testing, it appears the management of the Standard Criteria Method (SCM) and Marginal Criteria Method (MCM) testing would be somewhat difficult to track. In order to implement this guidance, a company will need to create new systems to track the manufacture and release of product. The implementation of new systems can be a huge burden and very costly, especially if a company's products have already been demonstrated to be well in control."

From what these commenter has stated, "Once we begin manufacturing batch testing," it would seem to any knowledgeable prudent person that the commenter's firm is not currently inspecting each in-process batch of drug product during manufacturing at each significant phase as the CGMP regulations clearly require for in-process materials and in-process drug products.

To the extent that this is the case, this manufacturer is engaged in the manufacturing and sale of adulterated drug products under **21 U.S.C. 351(a)(2)(B)** and, therefore, said drug products and persons are subject to legal action under **21 U.S.C. SUBCHAPTER III—PROHIBITED ACTS AND PENALTIES** (Sections 331 through 337).

Since this guidance, when issued, only suggests one way that a firm can comply with the clear in-process requirements set forth in the CGMP regulations for finished pharmaceuticals, **21 CFR Part 211**, the commenter's firm is free to use any fully CGMP-compliant system or procedure (*that they have proven does fully comply*) to assess the uniformity of each in-process material in each batch (**21 CFR 211.110(a)**) at each stage ("significant phase") of manufacture and release or reject that material as required by **21 CFR 211.110(c)** using "valid in-process specifications" (**21 CFR 211.110(b)**).

If, *once this draft guidance is finalized*, you find that it fully complies with all of the requirements set forth in **21 CFR Part 211** with respect to assessing the uniformity of in-process materials and the in-process drug products produced from them for their active uniformity, then your firm may elect to use the final guidance furnished provided your firm uses similarly valid approaches to assess the uniformity of the on-process materials and in-process drug products for other critical variable factors whose characteristics may be variable as a result of the allowed variation in the inputs used to manufacture them and/or the variation introduced into said materials and drug products by the processing and process control systems used the manufacturing of each of said entities. [**Note:** If your firm's review of the final guidance finds that it does not conform to all of the applicable CGMP requirements, then, your firm cannot follow the guidance provided. This is the case because, *as the Courts have repeatedly ruled*, your firm cannot use the FDA's actions or inactions, as an excuse for your firm's failure to comply with any applicable clear binding regulation.]

If your firm finds the final guidance fully complies with all applicable clear regulations and elects to follow the final guidance provided, and your firm finds that keeping track of the current inspection stage manually is a problem, this reviewer would suggest using a proven "**21 CFR Part 11**"-compliant computer program to perform this task which, to a properly programmed computer, is child's play. [**Note:** Such proven computer programs should be readily available as "staged' inspection has been widely used since the 1940's.]

As to the commenter's last statement, "The implementation of new systems can be a huge burden and very costly, especially if a company's products have already been demonstrated to be well in control," this reviewer suggests:

1. *Provided your firm already has a fully CGMP-compliant system that has been proven to assess the uniformity of each batch of drug product during manufacturing for each in-process material (e.g., preblend, dried/milled/blended granulation, coated material [beads], intermediate blend, and final blend) and the drug product (e.g., formed dosage units, coated formed dosage units, printed coated formed dosage units, a finished dosage units that comprise the drug product) that assess all critical variable factors in each material (e.g., for non-discrete materials, active(s), release agent(s), flow agent(s), stabilizer(s), dye(s)) or drug product (e.g., active (s), availability of the active(s), water, residual solvents, impurities, stabilizer(s))*, you need not change from your current proven system.
2. If your current system is not fully compliant, you need only develop a proven system that is fully CGMP-compliant.
3. If you have not been fully complying with **21 CFR 211.110**, **21 CFR 211.160,** and **21 CFR 211.165,** then your firm probably lacks the batch data needed substantiate the validity of your statement, "especially if a company's products have already been demonstrated to be well in control," because, instead of batch data, your firm's meager (compared to the number of units in your batches) samples' data lacks the statistical power to establish the nature of your batches with a high degree of confidence (a confidence level of 95 % or higher).

"The following are some scenarios that are likely to occur in a typical manufacturing/testing organization:

a. In general, a company will test first in-first out (FIFO), but on occasion business requirements may require a company to test out of sequence. For example, it is not atypical for a company to produce both a branded and a private label product (having the same formulation). The order of manufacturing may be to produce the brand first, followed by a campaign of the private label product. Due to a change in the Sales/Marketing Department's forecast, a company may need to release the private label product first. Based on the product requirements, the laboratory will test the private label product before continuing testing on the branded product in order to get it released. The products are the same formulation and the only difference would be tooling used in compression. According to the guidance, we would be required to (or due to the switching rules requirements, it becomes more important to) test the branded product before we could test and release the private label to ensure the SCM requirements were met. If the requirements were not met, we would need to switch to the MCM requirements for the next 5 consecutive batches, which could include the private label batches we are trying to release. This would put an unnecessary strain on a company and how the company does business. A company would not be allowed to respond to any changes in the forecast. This has a potential negative impact on consumers if the company is unable to supply to meet customer needs and an organization may lose some of their competitive edge. I am certain the intent of this guidance was not to put some companies at a disadvantage, to limit an organization's flexibility or to minimize an organization's ability to respond to market demands."

As you have noticed, the draft guidance clearly does not comply with the CGMP regulations that clearly require the inspection (*representative* sampling and *representative sample* testing) of each in-process material including the final blend with a release of each material by your firm's quality control unit before it can be used in the next step.

Moreover, under the scenario you have outlined, it would behoove your firm to develop your formulations to the point that your final blend's estimated batch RSDs for the active that are less than 2 % (which translates into an observed RSD on a *representative set* of unbiased blend samples (tested in duplicate for the active) of typically not more than (NMT) 1.5 %. [**Note:** To do this, your firm probably needs to establish sampling from the IBCs as your final-blend control point and sample multiple-dose aliquots of sufficient size for all of the possible testing for all of the critical variable factors in the final blend (minimally, the active(s), lubricant(s), and release control agent(s)). Provided your sampling is carefully controlled, the appropriate testing of duplicate aliquots from each sample for each critical factor (*or its surrogate* {e.g., for the lubricant, Magnesium Stearate, Magnesium is the surrogate; for stabilized Penicillin V Potassium, where granulation with Sodium Citrate is used to stabilize the Penicillin V Potassium or the release-control agent Sodium Starch Glycolate, the Sodium level; and for "polyols" use to regulate release, solution viscosity or refractive index}).]

While the batch RSDs for release control agents and stabilizers need to be similar to those for the active stabilizers, the acceptable RSDs for the lubricant can be significantly higher than the limits for the active(s) *provided the level of the lubricant does not significantly impact dosage unit performance*.

If your final blends were as uniform as outlined above and your "final blend" results used (as this reviewer outlined in an example earlier in this review in response to comments made by another commenter) to set the "Inspection" level for the dosage units, then the "passing" final blends could be released and, provided your firm's batch control system was modified to assign the final blend a batch number independent of the drug product batch number, you could then assign the sequentially released final blends to the drug product batches in what ever order your customer needs dictated. [**Note:** In this system, the blend batch is assigned to whatever drug product batch you use it to produce ("branded" or "private label").]

Moreover, *if your final blends were designed to be truly as uniform as the suggestions furnished by this reviewer*, your firm's critical control point should be the ***final blend*** – with all accepted ***final-blend batches*** being assured of producing dosage units batches that, *baring operator error or mechanical failure*, should consistently meet the least acceptable level of inspection for that drug product.

Operating in the manner suggested should assure that you can fully comply with the clear in-process requirements of the CGMP regulations without severely impacting your production flexibility.

If your firm can become more "on target" oriented and less "meets limits" oriented and, *as this reviewer has outlined in this report and in his previous formal comments to this docket*, establish truly "scientifically sound

and appropriate specifications, standards, sampling plans, and test procedures," then your firm should have no problem producing "batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release (**21 CFR 211.165(d)**) – not the post-release non-statistical "**any article in commerce**" sample specifications of the **USP** that many firms, including yours, seem to be non-compliantly using to release batches of drug product instead of complying with the clear requirements set forth in **21 CFR 211.165(d)**.

With respect to your remark, "If the requirements were not met, we would need to switch to the MCM requirements for the next 5 consecutive batches, which could include the private label batches we are trying to release," this reviewer agrees with you that the switching rule proposed here is statistically flawed (*because only a few dosage units are tested*, the outcomes of a single batch should not, by themselves, trigger a switch to more extensive inspection [**see** ANSI Z1.9's discussion of a statistically valid set of "switching rules" appropriate for use when a *batch-representative* set of samples is tested]).

In the example plan presented earlier in this report, this reviewer includes a "better switching rule" for switching from a "REDUCED Inspection" ("Stage 1") plan to a "NORMAL inspection" (Stage 2") plan based on two (2) "REDUCED Inspection" non-conformances in any five (5) consecutive accepted batches.

"b. At times, product may be held due to a pending investigation, which does not impact any other lots and has nothing to do with the blend process at the point in time that it is held. Depending on the type of investigation, the analytical laboratory may not receive samples of that lot at that time. The manufacturing team continues to produce additional lots and the testing is completed on those lots. According to this guidance, we would not be able to release those later lots until the lot under investigation was tested and released. Once again, there is an impact on how we release products."

While this reviewer understands your point of view, this reviewer knows of no investigation of a current lot that does not, directly or indirectly, impact other lots.

Further, investigations that have nothing to do with the blending process should, *provided your firm is fully CGMP-compliant*, be quickly resolved.

Moreover, the CGMP regulations do not require a firm to hold up the release of "later lots" or, for that matter, extend the investigation of prior lots, whether released or not, provided your firm has proven that the "problem" batch, *regardless of the phase at which the "problem" was identified*, is truly an isolated "problem" that cannot or has not affected any prior or subsequent lot.

However, neither the guidance nor the CGMP regulations permit a firm to continue manufacturing until the "problem" in the "problem" batch has been properly identified and proven to be localized to some identified "isolated" aspect of the manufacture of that batch.

"c. The guidance does not address dosage-proportional drugs. If the drugs are made from the same blend and a problem is seen in one dose and not the other…are both drug products suspect? For instance, a company may manufacture an 80 mg tablet and a 120 mg tablet from the same blend. A company would test the 80 mg tablets, that were compressed first, and, if the results were acceptable, would release the 80 mg strength. After the release of the 80 mg tablets, the company finds that they fail the SCM requirements with the 120 mg strength. What implications are there to the strength (80 mg) that was released previously? It is very typical for products to be prioritized by need in the laboratory and released based upon this priority. It is not uncommon, then, to release different dosage-proportional strengths of a product weeks apart."

This reviewer cannot resolve this scenario because it does not clearly outline the constraint conditions in sufficient detail.

Examples of the ambiguities include:

- Does the commenter mean that the 80-mg strength tablets made from "Blend A Part 1" were found to be acceptable for release at Stage 1 ("REDUCED Inspection")?
- Did the "Blend A part 2" that did not meet the "Stage 1" acceptance criteria meet the "Stage 2" acceptance criteria? Or did it fail?
- Was the problem with the "Blend A Part 2" in the last tablets produced?

Since the implications depend upon the details not provided, this reviewer cannot guess what the implications could be.

However, this reviewer would suggest that your firm should strongly reconsider your firm's implied practice to "release different dosage-proportional strengths of a product weeks apart" even when they were produced from the same batch of final blend. [**Note:** Having directed Quality Control operations for a small generic manufacturer who operated in a similar flexible manner, optimum productivity was attained by campaigning drug-product testing and release evaluation on a "by product" basis, regardless of the product's strength rather than testing different strengths made from the same blends several weeks apart – a practice that increases the setup and changeover overheads, reduces overall laboratory productivity, and, as you note, can lead to post-release problems if such are released on a piecemeal basis or inventory overhead increases when the "conditionally released" first part is held until the release status of the second part (the condition for "conditional release" of the first part) is resolved (a lose-lose-lose approach).]

"4. The guidance document fails to consider the importance of performing a solid investigation and the role that the results of that investigation might have on whether or not switching to a tightened inspection process is appropriate. Many investigations are quite lengthy and take some time to determine root cause and appropriate corrective action. I think it is onerous to assume that a company should automatically switch to tightened inspection based upon the test results irrespective of completing their investigation. The investigation, once complete, may identify a root cause that has no impact on subsequent batches of product. Any additional testing on subsequent batches would be costly, would be of no added value, and would simply be considered "waste". Also, while the investigation is ongoing, the company is continuing to produce product. A company certainly can't stop testing that additional product while it waits for the investigation to be completed.

This reviewer does not agree with the commenter's unsupported statements with respect to:

- A "solid investigation"
- "Tightened inspection"
- "Lengthy" investigations
- "Take some time to determine root cause and appropriate corrective action."

because these all point to a firm that:

- ✓ Has inadequately defined and/or controlled component acceptance criteria and/or practices (**see 21 CFR 211.84** and **21 CFR 211.160**),
- ✓ Has not properly developed the manufacturing process (inadequate manufacturing procedures, poor formulation practices, and/or poor development targets for an acceptable drug product)
- ✓ Does not truly understand and/or adequately control all of the processing variables that affect the material produced by each manufacturing step,
- ✓ Has not developed and established valid (*scientifically sound* and *appropriate*) in-process specifications for each in-process material and in-process drug product
- ✓ Does not sample unbiased *batch-representative samples* from *each* in-process non-discrete material and in-process discrete drug product used to manufacture *each batch*.
- ✓ Does not test duplicate unbiased unit-dose (or smaller) from each non-discrete sample with appropriate multiple-measurements of analyte response.
- ✓ Uses test procedures that are not the most appropriate for measuring uniformity of the variable factor or factors in the *representative* samples sampled.
- ✓ Fails to take a adequate number of batch-representative dosage units that is sufficient for a reserve and 3 times the number of dosage units required for all possible testing for all the critical variable factors in the drug product.
- ✓ Fails to have a comprehensive, multi-stage testing plan for each critical variable that starts at the "NORMAL" level of the "Process Variability Unknown—SD" in ANSI Z1.9 and proceeds therefrom to the "REDUCED" level of the "Process Variability Unknown—SD" when all the ANSI Z1.9's switching conditions permit that switch or, when continued problems are found at "NORMAL" level, switches to a "Process Capability" approach that requires doubling the "NORMAL"-level number of dosage units tested.

Having, *in one year*, improved the certainty in finding the root cause of a batch problem from below "50 %" to near "100 %," reduced the "OOS" side of that equation from days to typically less than one shift and reduced the production investigation time from "weeks" to typically less than "3 days," *in a less than cooperative environment*, this reviewer knows that any investigation that takes more than "48" hours to determine to the probable root cause(s) for the problem or problems observed takes that time because of a deficiency in the firm's understanding of the components, controls, specifications, and/or processes required to continually produce acceptable batches of drug product.

With respect to your soliloquy, "I think it is onerous to assume that a company should automatically switch to tightened inspection based upon the test results irrespective of completing their investigation. The investigation, once complete, may identify a root cause that has no impact on subsequent batches of product. Any additional testing on subsequent batches would be costly, would be of no added value, and would simply be considered 'waste'," this reviewer finds the following "final blend" realities:

- *If the "SCM" and "MCM" plans had batch decision validity*, the switching from "SCM" to "MCM" is a switching from a "REDUCED" to a "NORMAL" inspection plan, and not as mischaracterized, "*tightened inspection*."
- To "investigate" any "SCM" failure to meet its specifications for a particular batch, "MCM" testing must, for the reasons outlined previously, be conducted on that batch – to confirm ones findings, "MCM" testing should be conducted on at least one prior and one subsequent lot, regardless of whether one switches to the "MCM" plan as the basis inspection plan.
- An investigation may also identify a cause that requires the firm to cease manufacture of that product completely or to make significant changes to the requirements for one or more components, the processing steps, the current inspection plans, etc. – and so?
- If your testing program truly has developed and used the most cost-effective analytical procedures for assessing uniformity (**big ifs!**), then the incremental costs of the additional testing on any batch are just that incremental.
- *Up to the point that you have tested "1 %" of a batch*, additional testing, *when warranted (as it is when there has been a "non-conformance")*, is always valuable because it improves: **a)** your understanding of the true nature of the batch (acceptable versus unacceptable) and **b)** your "validation" of the true nature of your valid, CGMP-complaint manufacturing process for that drug.
- *Provided the "SCM" and "MCM" inspection plans were valid for making batch assessment decisions (and those in the draft guidance definitely are not)*: *For the case where you are experience frequent (>1 in 10) failures of the blend of a batch to meet your CGMP-compliant "REDUCED" inspection criteria*, then it would be more effective (if you were following the published Draft) to test all final blends under "MCM" (all three aliquots) because doing so would: **a)** provide "quasi-within-location" variance measures and **b)** avoid the issue of "between-test set" variance (improved batch characterization) as well as **c)** reduce test set setup and changeover costs (a cost reduction). [**Note:** The reviewer's alternative "final blend" inspection plan (inspect unbiased duplicate "unit dose" aliquots {using a procedure that provides a measure of the response uncertainty} from an unbiased sample from sufficient locations to span the batch), *a batch-representative "final blend" sample set with the "routine" samplings being conducted on the IBCs*, is not only *scientifically sound* and *appropriate* but

also provides the sound measures of the variances (random error, test measurement, within-location and between-location), associated with the values observed, required to properly assess the batch uniformity of such "final blends" from the calculated result values.]

"It would appear to make more sense to apply the switching rules once the investigation is complete and has identified a systemic problem that may impact future product. Any product that is already produced and been tested and shown to pass would need to be considered "good" (after all it did pass fairly rigorous testing). The switch would take place on product manufactured after the investigation was completed to ensure that any corrective action was effective. Again, I believe that the investigation into a blend issue is absolutely crucial but I think it is premature to jump to the conclusion that all subsequent batches are suspect without having completed that investigation."

This reviewer agrees with you that the application of any "switching rule" should not be done blindly (as the example provided in this report clearly indicates).

Moreover, as the reviewer's previous remarks clearly indicate, the issue of the level of testing required for a given batch or set of batches implicated in or contingent to the investigation of a particular batch has nothing *per se* to do with the appropriate basis level for the ongoing inspection appropriate for "routine" use after the conclusion of an investigation.

As this reviewer has previously stated, the choice of the basis inspection level (NORMAL, REDUCED, or TIGHTENED/EXPANDED) depends on, *in order of importance*: **a)** underlying statistical distribution of the values being measured (uniform, normal or other), **b)** the true level of uniformity in the non-discrete material or discrete-dosage units being inspected, **c)** the consistency of the inputs to, processing in, and outcomes from the process, **d)** length and steadiness of the production run, and **e)** the associated risk of making a wrong decision (that the firm's Quality Control unit has established as being appropriate). – the outcome of an investigation most definitely impacts and is, in turn, impacted by these.

However, the commenter's remark, "Any product that is already produced and been tested and shown to pass would need to be considered "good" (after all it did pass fairly rigorous testing)," is problematic because none of the sampling plans or sample numbers proposed in the draft for the dosage units come close to providing *scientifically sound* and *appropriate* inspection for "routine" production batches much less the "fairly rigorous testing" parenthetically alluded to by the commenter.

Factually, all that any inspection does is determine the outcomes or the samples tested and, provided sufficient batch-representative samples are evaluated, predict, *at some level of confidence*, that the batch output is, or is not, acceptable for release to the next step or, if that output is the finished drug product, whether or not, at some confidence level, the batch should be released.

Thus, the product "shown to pass" has, in fact, not been tested and can only be, as the commenter points out, "considered 'good'" until the outcomes from the next test are available.

At the "final blend" phase, the sampling and testing plans proposed in the Draft are scientifically unsound, known to provide biased results with less than robust estimates of the true within-location variability since the initial sampling takes a probably biased sample aliquot that irreversible disturbs the powder in that

"location;" the second aliquot then takes a biased sample from this disturbed powder (a probably different mix than it was originally) from that "location" further disturbing it, and the "final" sampling takes a third aliquot from the "same" location from this twice disturbed "location."

Then, compounding the problem, the draft guidance initially proposes to only test the first aliquot so that there is no estimate of the within "location" variability (variance) in the Draft's "SCM" stage and when aliquots "2" and "3" are tested to complete the testing for the "MCM" phase, there is an, at best biased, estimate of the within-location variability and no bridging data that would, if available, reveal any between-test offset between the two sets of data.

Moreover, the generally appropriate ANSI Z1.9 Inspection Plans applicable to batches of dosage units specify a "**200 unit**" minimum for the "Process Variability Unknown—SD NORMAL Inspection" plan (ANSI Z1.9) for batches larger than 150,000 units and a "**50 unit**" minimum for the "Process Variability—SD REDUCED Inspection" plan for batches larger than 150,000 units.

Compared to the ANSI Z1.9's 95-%-confidence-level inspection plans of dosage units, the plans in the Draft are anything but "rigorous testing."

With respect to the commenter's "The switch would take place on product manufactured after the investigation was completed to ensure that any corrective action was effective," the "switching" issue being discussed, "SCM" to "MCM," is separate from the level of testing appropriate for the investigation and related batches – "MCM" or better would have had to been carried out on the batch that was a problem because it did not meet the "SCM" criteria and, *to verify that any "corrective" action is effective*, at least one prior and one subsequent batch would need to have "MCM" level testing (even when the "basis decision level" remains at the "SCM" level) to obtain some inkling as to whether, or not, the "corrective" action proposed were indeed effective.

However, *as this reviewer has repeatedly pointed out*, for the CGMP-required *batch* acceptance/rejection, for the primary uniformity characteristic tested, typically, active uniformity, the general "REDUCED" level should be "50," the general "NORMAL" level should be "200," and the general "EXPANDED" level should be "400" – the "10" and "30" units sizes proposed in the draft guidance are, *if at all "sufficient" numbers*, only appropriate for non-CGMP-compliant, **USP**-type "sample" decision making practices justified when the *batch* is not available and a decision is required as to whether or not the part of the batch that is available is acceptable or not. [**Note:** For extended-release drug products where the active percentage is 50 % or more of the dose, the *primary uniformity characteristic* should be: **a)** the variable factor(s) (or surrogate(s)) in the final blend that "control the release of the active(s)" and, in the dosage units, **b)** the active availability (generally, the drug-release profile under some consensus condition {usually, the **USP** "**Drug Release**" or "**Dissolution"** test conditions applied to the *appropriate batch-representative number* of dosage units instead of the 6 to 24 non-batch-representative units specified by the **USP** for the "in commerce," grab sample, articles that the **USP** test addresses with the batch-conformance limits on the windows positioned appropriately inside of the **USP**'s lifetime expectation ranges with an appropriate AQL for the percentage of non-conforming units that are allowed in the tested portion of an acceptable batch.}).]

"Again, I believe that the investigation into a blend issue is absolutely crucial but I think it is premature to jump to the conclusion that all subsequent batches are suspect without having completed that investigation."

While this reviewer must agree with the commenter here, this reviewer note that the opposite, jumping "to the conclusion that all subsequent batches are" not suspect, is equally "premature."

Factually, it is not possible to come to any definitive conclusion as to the acceptability of the *batch* based on the deficient blend sampling and testing procedures proposed or the testing 10 or 30 non-batch-representative dosage units manufactured thereform proposed *unless you believe that a 20 % or a lower confidence level in your decision is an acceptable confidence level* – one that meets the Agency's expectation of a "high level of confidence" or the CGMP regulation ***minimum***'s *scientifically sound* and *appropriate* confidence level – both of which generally require a minimum confidence level of 95 %.

Because CGMP requires a firm to produce uniform final blends that meet *scientifically sound* and *appropriate batch specifications* for uniformity of each critical variable factor, finding any batch that appears not to be adequately uniform immediately puts in question not only the non-conforming batch but also all prior and subsequently produced final blends whose status is pending until and unless your investigation proves that the non-conformance observed is truly isolated and has identified root causes that do not call into question any of the controls on, or the nature of, any of the components, processing steps, manufacturing instructions, in-process materials and the in-process drug product (i.e., operator error or equipment malfunction).

Thus, unless your investigation clearly establishes (proves) that the non-conformance observed for a final blend was solely caused by operator error and/or equipment malfunction [including the equipment that controls the manufacturing environment]) the finding of a verified non-conformance of any in-process final blend, of necessity, not only implicates other prior and subsequent batches at whatever their phase but also reduces the validity of your filed manufacturing process or, in some cases, completely invalidates your filed manufacturing process and the drug product approval upon which your filed process is based.

Therefore, when you find any confirmed failure of a final blend to be adequately uniform (as required to meet the minimum requirements established by the CGMP regulations), all of your final blends and the batches manufactured from them are automatically suspect until your investigation proves otherwise because such call into question the validity of your filed process.

"5. It is our understanding that if we adopt this guidance, the Agency would expect us to establish verification of manufacturing criteria for our currently approved products. This would be an overwhelming task to complete all the required sampling/testing to show control of a process that we have considerable history on."

Since guidance cannot compel your firm to take any course of action, you may continue to follow your CGMP-compliant "verification of manufacturing" practices, if you have such in-process practices that meet the clear in-process, each-batch requirements set forth in **21 CFR Part 211**.

If your firm is not complying with any of the clear CGMP minimums, including those established in the CGMP regulations for in-process materials and in-process drug products in **21 CFR Part 211**, then your firm has a serious problem.

The CGMP regulations clearly require your firm "to show control of a process," to use your words, on *each batch*.

Under CGMP, **your firm must have and follow in-process control procedures on *each batch* that** "monitor the output" (inspect) and, *based on that inspection*, "validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product" (**21 CFR 211.110(a)**).

Under **21 CFR 211.110(b)**, "Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications," **your firm is required to: a)** have valid "in-process specifications for such characteristics" in your in-process materials and in-process drug products that may be variable, **and b)** examine and test *scientifically sound* and *appropriate samples* of *each batch* of each in-process "drug product and in-process material" in a manner that ensures that the *batches*, not just the samples tested, conform to said valid (*scientifically sound* and *appropriate*) *specifications*.

Under **21 CFR 211.110(c)**, "In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods," **your firm must test *each batch* of** "in-process materials for identity, strength, quality, and purity" unless your firm can prove that such testing is not appropriate (required) "during the production process" and your firm's "quality control unit" must approve or reject – not partially approve or conditionally approve each in-process material. [**Note: 21 CFR 211.165** clearly establishes the ***minimum*** in-process requirements for the testing and release for distribution of each batch of finished drug product.]

Under **21 CFR 211.1(a)**, "The regulations in this part (**21 CFR Part 211**) contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

Under **21 CFR 210.1(b)**, "The failure to comply with any regulation set forth in this part (**21 CFR Part 210**) and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

Given the preceding, since 1979, the law has required your firm to comply with the clear in-process CGMP minimums and provides no exceptions other than those spelled out in said regulations.

"Would it be acceptable to grandfather in currently approved products and only incorporate the required testing to support any changes to the process? Certainly, grandfathering of products that have higher proportions of active ingredient makes scientific sense as you would not anticipate a product that is substantially all active to display blend anomalies. Similarly, products that have demonstrated a long history of acceptable results, and where manufacturing issues and customer complaints have been minimal, would not seem to be good candidates for further levels of control."

Since the areas the draft guidance addresses are areas where there are and have been clear CGMP requirement ***minimums*** and, by law, the FDA cannot legally issue any guidance that does not conform to any clear regulation, no "further levels of control" are being or have been proposed and, equally important, the Agency cannot legally publish any document that does not conform to any clear regulatory requirement.

Thus, firms, such as yours, have already had up to 25 years to become fully compliant.

"The application of this guidance to currently approved and marketed products requires further discussion to ensure that the benefits of any additional work outweigh the significant burden to the organization required to adopt these controls."

If your firm does not clearly see the benefits of operating in a fully CGMP-compliant manner, then perhaps your firm and other like-minded firms should meet with the Agency and work out a consent decree that formalizes the costs of your firm's and the costs of the other like-minded firms' failure to fully comply with CGMP, as Schering-Plough did in 2002, so that your management and theirs, like Schering-Plough's, can clearly see and appreciate that the costs of compliance are truly far less than the costs of ongoing knowing non-compliance.

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

EMC-04[1] Comments By Pfizer, Inc., Posted 10 March 2004

The Pfizer comments begins by stating:

"Pfizer would like to acknowledge the effort put forth by the FDA in the publication of the Draft Guidance for Industry on Powder Blends and Finished Dosage Units–Stratified In-Process Dosage Unit Sampling and Assessment. We would also like to acknowledge the acceptance by the agency of the PQRI recommendations. It is recognized that a great effort has been made to incorporate the draft recommendations of the Blend Uniformity Working Group (BUWG) published in the PDA Journal of Pharmaceutical Science and Technology 57:59-74, 2003.

As a member of PhRMA, Pfizer has contributed to the preparation of the industry comments submitted by PhRMA to the agency. In addition to those comments we would like to submit the following five items listed in the table below."

Pfizer's reviewed comments are contained in a table that begins on the next page.

To conserve table space, Pfizer's "Section" and "Guidance Line" columns were merged when this reviewer evaluated Pfizer's comments.

[1] Documents **EMC-01**, **EMC-02**, and **EMC-03** have not been reviewed by this reviewer through his firm, **FAME Systems**, because said reviewer is the submitter of those documents to the Public Docket 2003D-0493 through the good offices of Ms. *Jennie Butler,* Director, Division of Dockets Management, Office of Management Programs Office of Management, United States Food and Drug Administration

Section G-Line	Comment / Observation	Rationale / Basis
IV.B 150-152	Add a reference to Attachment 1. There should be at least 7 samples taken from each of these locations for a total minimum of at least 140 samples. (See Attachment 1.) In general, this reviewer cannot agree with the original text much less the addition of a reference to Attachment 1 in an effort, *based on the rationale furnished*, to limit the number of samples to be tested for active content to a number less than the 140 dosage units sampled. This the case because the sampling plans proposed are, in general, not *scientifically sound* and *appropriate* for the evaluation of active content much less for the sampling scenario (dynamic sampling) unless: **a)** the equipment used has either exactly one or seven dosage-forming stations and **b)** there are no other critical variable factors that must be evaluated. [**Note:** In general, other factors (e.g., active availability, weight, water content, residual solvent level, impurities, stabilizers, lubricant level) may be critical factors that should also be assessed.] This reviewer also rejects the premise that determining the uniformity of the active is sufficient to assess the uniformity of each batch when, in fact, all know that it is not – active content uniformity and batch uniformity are not synonymous!	Without the attachment, it implies that 140 samples must be tested. Contrary to the Draft's rationale, the valid minimum number of discrete samples to test should be no less than the applicable numbers in the recognized consensus standards that outline minimum, at the 95% confidence level, numbers to test and statistical batch acceptance criteria appropriate to the acceptance of various percentage of nonconformance to the specifications used. For single-variable-factor, "process variability unknown," "normal" sampling and testing plans, the minimum numbers are 200 *representative* units for batches larger than 150,000 units and 150 units for batches larger than 35,000 units. Thus, the "sampling plans" proposed do not even meet the CGMP minimums for assessing the active's in-process uniformity.
V.	Clarify whether blend uniformity and in-process dosage unit testing is required for all BE/biobatches or only for the full-scale batches or only batches that support implementing the stratified sampling method. Since the CGMP regulations specify assessing the uniformity and integrity of *each batch* of drug product and require assessment and release at the completion of each processing phase, the CGMP regulations clearly require *all batches* to be evaluated *at each phase of manufacture*. This reviewer therefore recommends that the guidance be changed to conform to the *clear* requirement ***minimums*** of the applicable CGMP regulations governing the assessment of a sufficient number of ***representative*** in-process material samples to **ensure the uniformity** and integrity **of each batch** – **NOT**: **a)** Content uniformity of the samples tested for their level of active in each batch or **b)** Batch uniformity of the active or actives in the blend or dosage units in each batch, **BUT:** The overall ***batch uniformity*** for ***all critical variable factors***, including the level of each active, the availability of all actives, content weight, and all other critical variable factors in a given drug product, in ***each batch***.	The commenter provided no rationale. Among other things, **21 CFR 211.110** states: "a) **To assure batch uniformity** and integrity of drug products, **written procedures** shall be established and followed that describe the in-process controls, and tests, or examinations **to be conducted on appropriate samples of in-process materials of each batch**. **Such** control **procedures shall be established to monitor the output and** to **validate the performance of** those manufacturing **processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include**, but are not limited to, the following, where appropriate: (1) **Tablet or capsule weight variation**; (2) Disintegration time; (3) **Adequacy of mixing to assure uniformity and homogeneity**; (4) **Dissolution time and rate**; (5) Clarity, completeness, or pH of solutions. (b) **Valid in-process specifications for such characteristics shall be consistent with drug product final specifications** and **shall be derived from previous acceptable process average and process variability estimates where possible** and **determined by the application of suitable statistical procedures** where appropriate. **Examination and testing of samples shall assure that the drug product and in-process material conform to specifications**. **(c) In-process materials shall be tested for identity, strength, quality,** and **purity** as appropriate, and approved or rejected by the quality control unit, **during the production process**, e.g., at commencement or completion of significant phases or after storage for long periods.

Section G-Line	Comment / Observation	Rationale / Basis
General Comment	Indicate if this guidance is applicable to other unit operations that occur before tabletting or encapsulation, for example fluidized bed bead or granule coating, which is immediately followed by encapsulation. This reviewer understands that, provided the draft is corrected in a manner that renders it CGMP-compliant and either: **a)** focuses the guidance on ONLY assessing the uniformity of the active(s) in the batch or **b)** widens it to properly address overall batch uniformity, a CGMP-compliant guidance should include a statement coupled with its factual basis that the guidance furnished for the in-process assessment of the *uniformity* of each batch: A. Is applicable to other unit-operations that meet the CGMP definition of "significant phases" B. *When Point "A" is met*, MAY be used or modified as appropriate provided the output of said "unit operation" or significant phase is intended to produce an adequately uniform material. C. Should be modified, as appropriate, to ensure that the "specifications, standards, sampling plans, testing procedures" and other process controls are *scientifically sound* and *appropriate*, supported by a valid body of data buttressed by appropriate distribution-free and normal statistical evaluation controls that establish that the output of each "unit operation" or significant phase is uniform. Based on the preceding, this reviewer recommends that the guidance simply state that, *provided the justification provided is scientifically sound*, the manufacturer **may** be able to apply the guidance furnished to other ***material producing*** "unit operations" that produce *uniform* materials and, in some cases, **may** be able to justify combining them into a single "significant" processing phase combine *provided they are not separated by time*. However, the output of each significant processing phase must be evaluated and released by the firm's QCU prior to the material's subsequent use.	A fluidized bed process can provide mixing such that a subsequent conventional blending step is not required. While this reviewer recognizes, as evidenced by the "scientific" studies performed to support the noncompliant guidance in this Draft, that it is easy to misuse statistics, this reviewer also knows that the proper application of first distribution-free statistics and then, *when sufficient data and understanding is acquired and the process reaches the point that the output of each process* ***material-producing*** *"unit operation" is uniform*, the proper application of "normal" statistics can be used to describe the uniformity observed and required. Then, such valid statistical procedures can be used to set *appropriate* sample and BATCH *specifications* and/or *acceptance criteria* for the output of each ***such*** "unit operation." When that level of understanding of each ***material-producing*** "unit operation" is reached, the firm may be able to then appropriately combine ***such*** "unit operations" ONLY when they proceed without interruption from one such to the next provided the process of going from one ***such*** "unit operation" to the next does NOT risk introducing a significant non-uniformity in the material produced by each prior "unit operation" in ***such*** combined operations. In cases where there is a delay between operations and that delay may lead to significant non-uniformity, ***such*** "unit operations" cannot be considered a significant phase because they are separate (time-separated) phases. It is therefore incumbent on the submitter to justify whatever course of in-process action that it asserts is CGMP compliant. All in-process controls must meet **all** of the applicable "each batch" component, in-process, and drug-product CGMP ***minimums*** **in 21 CFR Part 211**.

Section G-Line	Comment / Observation	Rationale / Basis
Glossary 459-460	Provide a better definition of "exhibit batch" In keeping with the 12 March 2004 changes to the Agency's **CPG 7132c** that addresses the Agency's current views in process validation requirements in Sec. 490.100, titled "**Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval** (CPG 7132c.08)," this reviewer proposes replacing all references in this guidance to exhibit batches or validation batches with the policy guide's term, "**conformance batches**" which *means* any batches that are produced to demonstrate the agreement of the process outputs with their expected specifications and established acceptance criteria. In addition, this reviewer suggests that all should carefully consider the statement in that updated policy document that discusses "*process validation*": "Validation of manufacturing processes is a requirement of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.100 and 211.110), and is considered an enforceable element of current good manufacturing practice for active pharmaceutical ingredients (APIs) under the broader statutory CGMP provisions of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product. **The proof of validation is obtained through rational experimental design and the evaluation of data, preferably beginning from the process development phase and continuing through the commercial production phase**." Thus, as of March 2004, the Agency's position is that validation should begin in the process "**development phase**" (Design Qualification [DQ]) and should continue "**through the commercial production phase**" (Maintenance Qualification [MQ]). Thus, *process validation* does **not** stop, as many firms currently do, at the "Performance Qualification (PQ)" stage. The Agency's current position seems to be fully aligned with the "to monitor … and to validate …" requirements for each batch as set forth in **21 CFR 211.110**. (Continued on next page)	Exhibit batches need to be clarified for NDA applicants. This reviewer's rationale for the change suggested is contained in the reviewer's remarks.

Section G-Line	Comment / Observation	Rationale / Basis
	(Continued) Moreover, the amended guide continues with: "Before commercial distribution begins, a manufacturer is expected to have accumulated enough data and knowledge about the commercial production process to support post-approval product distribution. Normally, this is achieved after satisfactory product and process development, scale-up studies, equipment and system qualification, and the successful completion of the initial conformance batches. **Conformance batches** (sometimes referred to as "validation" batches and demonstration batches) **are prepared to demonstrate that, under normal conditions and defined ranges of operating parameters, the commercial scale process appears to make acceptable product. Prior to the manufacture of the conformance batches the manufacturer should have identified and controlled all critical sources of variability.**" Based on the preceding, this reviewer suggest that the definition of "**Exhibit Batches**" be deleted and replaced with: "**Conformance Batches** refers to any batch produced to demonstrate, and that does, in fact, establish the agreement of the process outputs with their established CGMP-compliant *specifications* and *acceptance criteria* which is required to be, or should be, submitted to support any DMF, VMF, IND, ANDA, NDA, or, when within the purview of the CDER, BLA. This includes any, test, biobatch, clinical batch, scale-up batch, technology-transfer batch, initial-process-qualification batch, change-supporting batch, and commercial production batch that are required to be or should be included with any process-related submission to the Agency."	
General Comment	Indicate that this guidance is not intended for PAT method use. This reviewer agrees with the commenter's suggestion here.	The regimen described in this guidance is not designed for PAT guidance. This reviewer supports the commenter's rationale here.

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

EMC-05 Comments By GlaxoSmithKline, Posted 10 March 2004

The GlaxoSmithKline comments are the same as in the comments in their "**C-02"** that has been reviewed.

Therefore, this reviewer refers the reader to that review.

EMC-06 Comments By PQRI, Posted 10 March 2004

The PQRI document posted here is simply a listing of the documents submitted in the PQRI's formal submission posted as **C-04**.

Therefore, this reviewer refers the reader to that review.

EMC-07 Comments By KV Pharmaceutical Co., Posted 10 March 2004

The posted KV comments have no cover or introduction.

KV's reviewed comments are as follows:

"1. In Scope (67-71), the document states that 'traditional powder blend sampling and testing' can be used to comply with cGMPs. This, or another document, should address minimum requirements for industry to document that the traditional approaches in use meet the burden of cGMPs. For example, does this infer that unless traditional approaches can correlate blend sample data with finished product data, the agency will deem the approach inadequate?"

This reviewer's short answer is that, *unless your traditional approaches are fully CGMP compliant*, the Agency should find your procedures inadequate.

In addition, *when your traditional approaches are fully CGMP compliant*, unbiased *batch-representative sample* amounts of the material from each significant phase of manufacture will be sampled and an *appropriate batch-representative* number of unbiased "unit dose," or smaller, aliquots will be tested, found to comply with your *scientifically sound* and *appropriate* in-process *sample specifications* and *batch acceptance criteria* (not the non-applicable **USP** criteria) for each critical variable factor (including, but not limited to, *active uniformity*), and the acceptable in-process batch will be released by your QCU for use in the next manufacturing phase for which the material is approved for use.

When you truly do accomplish the preceding for each significant in-process manufacturing phase, then the estimated distributional properties for the blend (including the blend's mean, RSD, and range) will be comparable to the distributional properties for a set of *batch-representative samples* from the finished drug product batch (mean, RSD, and range) and both sets will be within the process envelopes established for each material during the development of your manufacturing controls and procedures.

"In other words, the current industry approach may demonstrate process adequacy by showing the Beginning, Middle, and End blend samples and a typical content uniformity analysis (10 samples from across the batch) meet requirements. In this document, the minimum number of tests to establish the same conclusion is 30 blend and 60 tablets samples. Will FDA accept out historical approach as meeting traditional requirements or judge it as inadequate?"

Provided:

1. Your developmental studies have established that these three samples are truly *representative* of each batch your final blend and sufficient to capture the non-homogeneity, if present, in the final blend.
2. Your process has properly evaluated and your QCU has released all components, and materials (e.g., pre-blends, granulations, coatings) used to fabricate the final blend.
3. Your final blend forming process is CGMP-compliant, followed, and transpires without incident (or, if there is any incident, it is properly investigated and resolved).
4. Your Beginning, Middle, and End blend samples are unbiased samples of sufficient amount to perform all possible replicate testing (typically, 6X or

larger the aggregate of all independent tests) for all critical variable factors, including but not limited to any:

a. Active pharmaceutical ingredient (API)
b. Lubricant (Lube) added to aid material transport through the dosage forming step,
c. Component that is added to mitigate or control (retard or accelerate) active availability in the dosage units (Release Mitigator),
d. Stabilizer added to stabilize an active or any other component (Stabilizer),
e. Other variable factor whose level your development studies have found can adversely affect the performance of the drug product and
f. Any physical properties assessment required.

5. You test components "a" through "f" in duplicate and with sufficient measurements on each aliquot to "average out" measurement uncertainty.
6. Your valid results for each unbiased sample find that the mean range for all duplicates is within the experimental error uncertainty introduced by the test.
7. For each critical factor, the difference between the means for your valid means for each sample is not greater than your testing error for each test
8. The overall means for each critical factor other than the active are within their established variability ranges, and
9. The overall mean for each active is:
   a. Not less than 100 % of the final label claim or, if higher, your nominal target content level (to satisfy **21 CFR 211.101(a)** or
   b. If less than the level in "6.a," not less than 99 % of the level in "6.a" provided your approved process provides for a small dosage-unit target adjustment to compensate for the deficiency found in "6.a."
10. Your records show that this final blend was prepared in accordance with your FDA-approved process and no processing problems occurred, or, if any may have occurred, all such have been investigated and resolved in a CGMP-compliant manner.
11. Your QCU has reviewed all batch records and associated information and released the batch of final blend for further processing.
12. Your dosage-forming operation follows your approved CGMP-compliant procedures for dosage-unit production and inspection (sampling, examining, and testing) that:
    a. *If you do dynamic sampling*, furnishes sufficient batch-representative dosage units from each sampling point (typically, not less than 3 X the number of dosage-forming stations used in the dosage-forming operation from each dosage-forming machine used) established (routine and restart) and collects each sample separately, *or*
    b. *If you statically sample from the entire batch at the end of the dosage forming operation*, furnishes not less than 200 randomly selected (in a manner that ensures the samples are from every part of the batch whether the dosage units are collected in a single container or multiple intermediate dosage-unit-holding containers [IDUHCs]) dosage units for each critical variable factor that is independently evaluated using a destructive test.

13 Your QCU's laboratory properly evaluates your formed dosage units for all critical variable factors using the appropriate ANSI Z1.9, or larger, number (typically, that minimum number is not less than [NLT] "50" when your firm can justify using "reduced" inspection and NLT "200" when "normal" inspection is required) of batch-representative dosage units for each critical variable factor that is assessed in an independent test including but not limited to:
   a. Each active,
   b. Active availability ("drug release" or "dissolution") or the level of the release-mitigating agent
   c. Dosage unit content weight
   d. "Assay,"
   e. Any other variable factor that the FDA (or the **USP**) deems critical.

14. Your QCU evaluates the valid results from the appropriate testing against the scientifically sound sample specifications and batch acceptance criteria that are appropriate for the *batch* (while derived from the **USP**'s expectations, these cannot be the **USP** criteria and, where the USP or the FDA sets lifetime post release criteria, these must be appropriately inside of the lifetime criteria established by the **USP** or the FDA) *including but not limited to, in general*:
   a. Batch active level NLT 100 % of label claim of your firm's higher target (to satisfy **21 CFR 211.101(a)** (based on either the mean of all active uniformity values assessed or the mean assay from the assay of not less than two aliquots from a homogeneous blending of not less than a *batch-representative number* of units [typically, NLT 200] or the direct assay of multiple preparations of equal numbers of **batch-representative** dosage units [whose sum is typically NLT 200 *batch-representative* dosage units]).
   b. All *batch-representative* dosage units evaluated for active uniformity are appropriately inside of your firm's established limits for each active (your established limits must be appropriately inside of the **USP**'s post-release lifetime "any article" expectation values)
   c. All *batch-representative* dosage units evaluated for either:
      i. Active availability are appropriately inside of your firm's established limits for the availability of each active (your established limits must be appropriately inside of the **USP**'s or the FDA's post-release "any article" expectation values) or
      ii. Level of the release mitigating ingredients meet your firms established limits for their variability that is sufficient to ensure that the finished dosage units will meet their established lifetime levels of active availability for all dosage units in the batch.
   d. All batch-representative dosage units evaluated for weight meet your firm's established limits for the weight of "content weight."
   e. All batch-representative dosage units evaluated for active availability are appropriately inside of your firm's established limits for the availability of each active.
   f. All batch-representative dosage units evaluated for any other critical variable factors are appropriately inside of your firm's established limits for the availability of each factor (your established limits must be

appropriately inside of the **USP**'s or the FDA's post-release "any article" expectation values)

15. Your QCU finds that your samples' results meet all of their specifications and the batch acceptance criteria that predict, *at a confidence level of NLT 95* %, the untested majority of the batch furnishes dosage units, when converted into finished drug-product dosage units, will meet the batch's lifetime expectations.
16. Your records show that this batch of dosage units was prepared in accordance with your FDA-approved process and no processing problems occurred, or, if any may have occurred, all such have been investigated and resolved in a CGMP-compliant manner.
17. Your QCU has reviewed all batch records and associated information and released the batch of final blend for further processing.

then, the Agency should accept your historical approach or, *if any of the preceding is not as stated*, the Agency should reject your historical approach on the basis that is not CGMP-compliant.

[**Note:** It is not up to the FDA to judge whether your approach is adequate, the Agency is charged with ascertaining whether, or not, your approaches are *scientifically sound*, *appropriate* (**21 CFR 211.160**) and your firm and its approaches are fully CGMP-compliant, or not.].

"The ambiguity regarding existing products needs to be clarified."

Hopefully, this reviewer's remarks have addressed the commenter's "ambiguity regarding existing products."

"2. In Scope (lines 95-97), the document indicates that extremely low or high dose products 'may call for more rigorous sampling than that described in this guidance….' A couple of comments: a) no reference or other scientific rationale or other guidance on sampling approach is offered and b) this may impact Industry significantly because the historical approach for products with high concentrations of active is to do less rigorous sampling and testing, as can be seen in the USP test for content uniformity for products containing 50mg or more of an active ingredient that compromises **(sic)** 50% or more (by weight) of one tablet where weight variation can be substituted for chemical analysis."

First this reviewer suggests that the commenter should reread the draft because it speaks to "low dose" and "high potency" products in this regard and not, as they represent, to "high dose" products.

Second, *by statute*, the CGMP regulations for finished pharmaceuticals apply to in-process materials and in-process drug products and not any **USP** protocol because, by statute, the **USP** and other recognized official compendia only apply to products in commerce.

Third, given that the **USP**'s laxity with respect to content uniformity on the class of drug products that you speak to, the determination of the active uniformity of the drug product at all significant phases of manufacturing (as it clearly required by the applicable CGMP regulations) is more important than it is for products where, post release, the **USP** requires *Content Uniformity* testing!

"3. In Scope (lines 136 – 141) does this mean industry must conduct any blend uniformity testing in triplicate to assess 'location variability'? Does this proposal apply to development phase or routine validation as well?"

To the extent that the CGMP clearly requires the assessment of the uniformity of the final blend of *each drug product batch* for all of its critical variable factors, including, *but not limited to*, active uniformity, it is incumbent on each manufacturer to accurately assess the uniformity of each blend in a *scientifically sound* and *appropriate* manner.

This draft guidance document simply suggests one of scientifically unsound way that a firm may consider in addressing the issue of the validity of the firm's assessment of the active level at each sample location.

While this reviewer would not recommend using this approach because it is at odds with the precepts of sound inspection science for complex material mixtures of limited mechanical stability (as the Industry continues to characterize the final blends that, *for some unstated reason*, they apparently choose to develop for use in the manufacture of their formed dosage units).

This reviewer recommends that the commenter should consider the general approach presented in his review of others who commented to the FDA Public Docket 2003D-0493 or that he presented in his comments to said docket.

"4. In Scope (lines 148 – 152 and 153 – 157) the two paragraphs are unclear since it appears that in addition to minimum 140 samples collected throughout compression, there is a requirement to collect 7 additional samples from "significant event" locations."

First, *as with any guidance*, this draft document does not set any requirements; it merely suggests courses of action

As the commenter has stated, this Draft does suggest taking additional samples from "significant event" sampling points.

The applicable CGMP regulations, on the other hand, do establish clear requirements that you must follow.

In **21 CFR 211.160(b)(2)**, "Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. **Such samples shall be representative and properly identified**," that clear requirement is that samples must be a *batch representative sample* (as the term *representative sample* is defined in **21 CFR 210.3(b)(21)**, "Representative sample *means* a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and **intended to assure that the sample accurately portrays the material being sampled**" [bolding added for emphasis]).

To meet the requirement, if a firm uses dynamic sampling as the draft suggests and many firms do, then, *contrary to the draft's guidance*, the samples sampled at every point including the "significant event" points when such occur, must be *representative samples* of the local variability (not less than 1 unit from each dosage forming station in the dosage-forming system or systems used to form the dosage units from the final blend) at each point of sampling as well as a sufficient in number for at least 3 times the number of units required to assess the uniformity all of the critical variable factors in the dosage units, including (*but not limited to*) the *active uniformity* subject to the

constraint that the *number sampled at each sampling point* must, *if the sample sampled is to be unbiased as it should be*, be an integer multiple of the number of dosage-forming stations in the systems forming the final blend into dosage units. [**Note:** If weight-screening equipment is part of the production systems, the samples should be collected prior to the weight screening.]

"5. In Scope (lines 160 – 162) besides physical transfers being considered 'significant events' in the blending process, what other things should be considered a 'significant event'? Blending time, order of addition, – they are all 'significant events' but the only assessment required is on the final blend."

A few of the other events that quickly came to this reviewer's mind which are "significant events," include, but are not limited to,

- ✓ Operator error,
- ✓ Power failure,
- ✓ Cover leakage on tumbling blenders or discharge valve leakage on all,
- ✓ Spills,
- ✓ Partial blender malfunction (e.g., agitator bar stops prematurely or does not stop when it is supposed to, or blend cycle terminates prematurely), and
- ✓ Loss of environmental control (e.g., temperature, humidity, dust, air flow) in the mixer area during any stage of the blending operation (e.g., component and material loading, mixing, blend unloading).

"6. In Scope (lines 179 – 181) in this comparison what is the rationale and how/what should acceptance criteria look like in a final summary?"

In response to the commenter's request here, this reviewer offers the following proposed revision for the bullet in question and a supporting rationale for that revision that hopefully addresses the concerns expressed by the commenter here:

"• Compare the *statistical uniformity inferences derived from the* results ~~of stratified~~ *observed for the dynamically sampled* in-process dosage unit analysis of a *batch-representative set of samples* from *the previous step* ~~with uniform content~~ *to the corresponding statistical uniformity inferences derived from the representative sample results from* ~~of~~ the finished dosage units ~~from the previous~~ tested for uniformity in *this* step. This comparative statistical analysis ~~should~~ *must* be done without weight correction."

The comparisons should be between the statistical inferences (e.g., means, variances, kurtoses, other derivative statistical values, and the probable ranges) and not between the values observed.

For some critical variable factors (e.g., active availability and water) that the in-process CGMP regulations require the manufacturer to monitor, the statistical inferences may indicate that there is a significant bias between the probable values for the in-process dosage units and the finished dosage units even when the results obtained are each from valid *batch-representative* sets.

As to the how/what should acceptance criteria look like in a final summary, this reviewer's answer is that these should be tabulated and the batch *acceptance*

criteria for each critical factor would be that the statistical values observed and their predicted outcomes values are, *within the residual uncertainties in the two batch-representative data sets*, the same.

However, this reviewer strongly counsels that the data sets must be truly *batch-representative* before a comparison of the data sets is valid.

Moreover, attempts to correlate a set of data results from the testing of biased unit-dose (or non-unit-dose) non-batch-representative final-blend sample aliquots (that, in most cases, do not "span the batch") to a set of data results from the testing of an insufficient number of non-batch-representative dosage units formed from that final blend is, at best, junk science.

"7. In Scope (lines 199 – 204) it appears that sampling from the blender is mandatory whether it is a scale-up lot or validation lot."

Though the draft guidance does only address sampling from the blender, nothing in a guidance document is mandatory – guidance suggests, it cannot compel.

That having been said, this reviewer finds that the commenter's perceptions otherwise are correct, this Draft does only address sampling from the blender which, *as the commenter points out*, is usually not the appropriate point in the production of a full-scale final blend that blend uniformity should be assessed because it is difficult to impossible to sample a *representative* set of *unbiased samples* directly from the mixer when the depth of material therein exceeds one (1) meter, as is typically the case at full production scale.

"It contradicts the earlier statements in this guidance concerning the fact that either blender or receiving container could be selected for sampling. While it might be appropriate to sample powder from blender or receiving container could be selected for sampling. While it might be appropriate to sample powder from blender during development phase in order to establish optimum time and correlation between blender uniformity and receiving container uniformity, it is definitely unnecessary to sample from the blender during validation lots manufacturing."

This reviewer agrees with the commenter's observations but notes that the Draft provided is based on a flawed recommendation report from the PQRI who apparently was more interested in continuing to promulgate blend inspection practices that the PQRI knew, should have known, or was responsible for knowing, were and are fundamentally flawed and, based on PQRI's own studies, were known not to and/or do not accurately assess that the uniformity of the blend.

Those flawed practices include, *but are not limited to*, recommending:

- Sampling multiple (three) unit-dose samples instead of a single multiple-dose (consisting of 10's to 100's of unit-dose amounts) sample at each sampling point.
- Sampling at full-scale directly from large-scale blenders when such samplings are not only difficult to "impossible" but are also known to produce "top biased" samples even when multiple-dose samples are sampled.

- Focusing on sampling from regions of "known" lower uniformity instead of recommending that the manufacturers comply with the clear CGMP requirement to use a sampling plan that takes *batch-representative samples*.
- Analyzing only one of the three replicate samplings initially so that there is no initial estimate of "within-location" variability for each biased result and then, *only when the "numbers" indicate that the some location is "different" from the others*, analyzing the other two samples. [**Note:** In addition, this guidance does not provide any valid guidance for the handling of the results when the initial set of values do not match the results from the other two replicates analyzed at a different date (a less than sound analytical "system" that further "muddies the water" because the approach used: **a)** knowingly, or unknowingly, ensures that there is no internal between-analysis-set sample estimates of bias) and **b)** is open to conscious or subconscious analyst bias.]

The apparent PQRI's "apparent reasons," *to this knowledgeable and experienced reviewer at least*, for ignoring the fundamentals of material inspection and proposing such scientifically flawed inspection plans seem to be, *based on their other previous and subsequent publications*, their single-minded and relentless campaign to discredit blend sampling to cover up and/or justify the industry's knowing failure to comply with the clear requirements of the CGMP regulations set forth in plain language in **21 CFR 211** governing in-process materials and in-process drug products.

In addition, the CGMP regulations for finished pharmaceuticals (drug products) require the manufacturer to "monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product," and requires that the following applicable parameters, and, where appropriate, unspecified others be monitored in each batch as follows:

"… control procedures shall include, but are not limited to, the following, where appropriate:
(1) Tablet or capsule weight variation;
(2) Disintegration time;
(3) Adequacy of mixing to assure uniformity and homogeneity;
(4) Dissolution time and rate;
(5) Clarity, completeness, or pH of solutions."

Thus, the PQRI's recommendation and this Draft, based on the PQRI's recommendation are fundamentally flawed because their titles and content falsely equate active uniformity to material uniformity when nothing could be further from the truth.

To address this issue, this reviewer submitted a "Revised Draft" that limited the guidance to guidance on assessing the active content in blends and formed dosage units.

Returning to the issues of what constitutes a scientifically sound and appropriate inspection plans (as required by **21 CFR 211.160**), this reviewer again offers his hands-on experience-based views gathered over more than two decades of experience in the development, improvement, and the initial and retrospective "validation" of manufacturing processes for both the active ingredients and finished products in the biocide and pharmaceutical industries.

Having overseen the sampling of full-scale blends from blenders with working volumes above 150 m^3 and, because of the density of the materials being blended, *material masses up to in excess of 2100 kg*, this reviewer knows that, at full production scale, *scientifically sound inspection plans* almost always obtain the *scientifically requisite unbiased samples* by sampling from the "50 kg" IBCs into which said full-scale blends are transferred and, where it is probative, from the material left in the discharge valve of the mixer after the emptying of the mixer.

Further, this reviewer knows, *having repeatedly demonstrated the validity of his position by comparative sampling from intermediate scale (15 m^3 mixers) blends (including pre-blends, dried/milled/mixed wet granulations, intermediate blends and final blends)*, that the best sampling plans take a *batch-representative number of samples* by taking a single sample (that is more than three [3] times in amount [typically, > 5 to10X] for all of the chemical and physical testing required to determine the uniformity of the blend at that sampling point for all critical variable factors [both chemical and physical] that must be evaluated ***to determine blend uniformity of the batch***) at each of the *batch-representative sampling points* in the inspection plan used.

Further this reviewer knows, *having repeatedly established the validity of this in the development and initial and retrospective studies that he planned and oversaw*, the analysis of each "blend" sample is best conducted by carefully

- **Transferring the multiple-dose samples sampled into a** suitable **container** that **it** "**fills**"
- **Sealing and carefully transporting that sample to a suitable test facility** (usually called a lab)
- Logging each sample set into that lab's tracking system
- **Having trained analysts sample duplicate "unit dose," or smaller aliquots**, **prepare the aliquots** subsampled **and evaluate the appropriate aliquots from said duplicate subsample preparations** for the number of times required to assess the measurement uncertainty
- **Critically evaluating all of the valid data** produced by those studies
- **Reporting all of the results along with their number and the result uncertainty estimates** (testing, within-location, between-location, overall) **and the evidence that establishes that each result reported is valid or not**.

In addition, previously in this review (of the comments of another commenter), this reviewer has provided a suggested sampling plan for sampling from "50 kg" IBCs and a hopefully CGMP-compliant set of staged inspection plans for both the final blend and the dosage units formed from it that uses the results of the final blend to set the initial level of inspection required for the dosage units produced from it.

These plans are based on the *sound inspection principle* that, *as the uniformity of a material declines*, the number of evaluated samples that are required to adequately define the material's uniformity increases as well as the *sound quality principle* that the costs of non-quality are minimized by detecting out-of-specification materials as soon as possible in a multiple-step process.

Hopefully, the preceding has provided the Agency and this commenter a better understanding of what the CGMP regulations require (and have required from the late 1970's) and CGMP-compliant approaches to complying with the requirement ***minimums*** established in **21 CFR Part 211** as they apply to assessing the uniformity of the active or actives in in-process materials and in-process drug products.

In addition, instead of "revising" the current CGMP regulations to "improve" them, this reviewer again cautions that the Agency should focus on getting the Industry to fully comply with the current requirement ***minimums*** that, *based on the guidance recommended by their "scientific" lobbying group, the PQRI*, the comments made to this docket, and other evidence, the Industry continues to knowingly ignore.

When the Agency is fully satisfied that the Industry is fully compliant, then the only sections of the CGMP regulations that truly need improvement should be reduced to "**Sec. 211.176 Penicillin contamination**" which needs to be broadened to address all highly toxic (e.g., chemotherapeutic agents and "botox") and/or highly bioactive drugs (e.g., steroids, and irreversible neurotoxins).

"8. In Scope (line 251 – 259) the described approach is extremely challenging to implement in terms of basic logistics. Why not just evenly space the process out and sample? By sampling the Beginning, Middle and End plus speed and hopper studies it would cover the significant events."

First, this reviewer recommends that this commenter should recognize that the procedures outlined in this Draft are guidance and <u>not</u> requirements; and the commenter should treat it as such.

As to the commenter's "plan," this reviewer recommends that, when the firm can prove that said "plan" is *scientifically sound* and *appropriate*, and complies with all applicable CGMP regulations, then, this commenter may use that fully CGMP-compliant "plan."

"9. In Scope (line 276) the proposed RSD limit of ≤ 4.0% is too restrictive. USP allows up to 7.8% for 30 samples with more restrictions placed on individual values. The entire concept of 'readily pass' vs. 'marginally pass' does not guarantee manufacturing of better products – just more testing."

This reviewer finds the commenter's remarks here unsupported by today's state of manufacturing science ("six sigma").

Moreover, this commenter seems to lack an understanding of the fundamentals of inspection science that properly tie the level of inspection to the uniformity of the material (the more uniform, the less testing).

If this commenter truly wishes to reduce the firm's in-process and release testing burden, then let this firm develop and enforce rigorous *acceptance criteria* for all of the critical variable characteristics of each component that can affect the blending of said components into the materials that directly or indirectly are used to form the final blend and use processing techniques known to produce highly uniform and structurally stable final blends that have a mean that is not less than 100 % of label claim (or, if higher, the "nominal" manufacturing target) and a batch RSD for the final blend that is less than 1.2 % for each active which they

then manufacture into dosage units that have a batch RSD of less than 1.8% for the active(s) in each tablet batch and not more than 2.1 % for the active(s) in each capsule batch. [**Note:** Having done this or better, this reviewer knows that these limits are doable.]

When aforesaid controls are met, a firm may be justified in only testing a few *batch-representative* blend samples (as per **21 CFR 211.110**'s "to monitor … and to validate …" requirements) and, *when the appropriate aliquots from said samples are tested for all of the critical variable factor properties that development studies have established as needing confirmation and found to meet the batch's established acceptance criteria*, testing only a few *batch-representative* dosage units for acceptance for release.

Only when you have *scientifically sound* proof that you have built quality into your products can you validly test a few samples.

As long as manufacturers, such as this commenter and the other commenters, incorrectly develop their products so that the testing of a few samples from batches of thousands or millions of dosage units will probably meet the **USP**'s post-release "any article in commerce" requirements instead of, *as they are required to do by the CGMP regulations*, develop, manufacture, and evaluate each batch so that each released batch is predicted, at a confidence level of not less than 95 %, to consist of dosage units that **all** should, *if tested*, meet all of the CGMP's release criteria (including those set forth in **21 CFR 211.165(d)**) and the **USP**'s post-release *expectation levels* – not the **USP**'s lifetime *permissible limits*!

Since most firms, *as this reviewer's experience has repeatedly found and this commenter's remarks seem to indicate*, set the wrong developmental targets, it is little wonder that they often produce such, *by today's* "*six sigma standards*," shoddy products!

"10. In Section VI. B. (line 284), the development instructs companies to utilize the Standard Verification method (SVM) described in Section VII. However, Section VII uses the terminology of Standard *Criteria* Method (SCM) with no mention of SVM. Also, a reference to MVM is included in line 385 (should be MCM)."

This reviewer agrees that the terminology should be corrected to be "self consistent" and, as other commenters have suggested, has gone along with the "SCM" and "MCM" naming even though, in standard inspection terminology, "SCM" corresponds to a "REDUCED" inspection level and "MCM" corresponds to a "NORMAL" inspection level which, for dosage units, should have been based on the applicable plans (process variability unknown—standard deviation) in the recognized consensus standards for inspecting batches of discrete materials (ISO 3951 and ANSI Z1.9) but these plans are not even mentioned simply because the number of units required by said 95-%-confidence-level consensus standards are larger than the numbers that the PQRI (and, their sponsor, the Industry) wanted to test – science be damned, propose the numbers we are testing or want to test even when these are not *scientifically sound* numbers.

"11. In Scope (line 310-315) is this procedure intended to replace normal release testing or, in case of coated products, supplements standard release with testing compressed tablets? What happened to randomization as a driving concept in any statistical section?"

Under CGMP, the driving requirement is that the samples sampled must be *batch representative* and, as the definition in **21 CFR 210.3(b)(21)** states "Representative sample *means* a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled"; when "random sampling" will produce a *representative sample*, it is one of the "rational criteria" that can be used.

However, unlike the non-representative sample approach introduced by the PQRI and used in the Draft, the CGMP regulations require the overall sample to be a *representative sample* of the *batch* – NOT, as this Draft proposes, a sample from those "locations" in the batch where the least uniform "areas" or "portions" are "expected" to be found.

"12. In Scope (lines 419 – 421) the proposal allows a company to take and develop their own approach to blend uniformity. How will the agency view a submission using a company developed testing schemes?"

As long as the company's inspection plans have been proven to be *scientifically sound* and *appropriate*, and these inspection plans fully comply with all applicable CGMP regulations (unlike this Draft), then the Agency should accept that company's inspection plans.

"13. Attachment 1 --- There is confusion about the "diamond" in lines 502-504 which states 'Is mixing problem identified?' This comes after analyzing 2nd and 3rd blend samples from each location. Criteria need to be listed in this diamond to direct how to proceed. For example, perhaps this should state that the RSD of this set of samples (10 +10 = 20) be less than 5.0% and all individuals within 10 % of mean. If so, proceed to 'yes' branch towards dosage units. If not, proceed to 'no' branch and conclude that the 'Blend is not uniform'."

This reviewer does not disagree with the commenter's request for more guidance here.

However, this reviewer knows that the fundamental sampling and testing approaches used are seriously flawed and, *until those flaws are addressed and corrected to the point that the inspection plans proposed are scientifically sound, appropriate, and, at each significant phase in manufacturing, fully comply with all of the clear applicable CGMP regulations governing in-process materials and in-process drug products*, cannot suggest what "directions" should be appropriate for this decision approach.

"14. Under this plan, is blend uniformity testing required for ongoing production if adequacy of the process is verified during development?"

Though the in-process CGMP regulations clearly require a manufacturer to monitor and validate the uniformity of each final blend, the draft guidance published by the FDA does not conform to this clear regulations and does "propose" allowing "ongoing production" to skip blend uniformity testing and use the "weight corrected" active results from the testing of a few non-batch-

representative dosage units as a biased surrogate for the uniformity of the final blend.

Hopefully, the FDA will heed the 1988 Supreme Court's directly applicable unanimous decision (Berkovitz v. USA) that prohibits the FDA's publishing documents that do not conform to any clear applicable FDA regulations and, as the Agency should, correct this draft document so that it does conform to all of the clear applicable FDA regulations including, but not limited to, the CGMP regulations.

"15. Overall, we feel the document could be written with more clarity. Several of our questions above should have been readily discernable, but were not despite repeated attempts to comprehend the proposal."

This reviewer agrees with the commenter here and hopes that, in addition to improved clarity, any revision will also be CGMP conforming.

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

EMC-08 Comments By Merck & Co., Inc., Posted 15 March 2004

The Merck & Company comments begins by stating:

"Merck & Co., Inc is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck fully endorses the importance of developing a manufacturing process that guarantees consistent blend uniformity. As such, we welcome the opportunity to provide comment to the important draft document intended to provide manufacturers with guidance for meeting the requirements for demonstrating adequacy of mixing. The following three critical comments are intended to address important considerations for the finalization of the draft guidance."

This reviewer cannot agree with the commenter's introductory remarks because, after correctly stating, "the importance of developing a manufacturing process that guarantees consistent blend uniformity," the commenter then mischaracterize the CGMP requirements as ones "for demonstrating adequacy of mixing" when the applicable CGMP requirement, *as stated in* ***21 CFR 211.110(a)*** (**bolding** added to emphasize the requirements that this guidance should be addressing), is "**To assure batch uniformity** and integrity of drug products, written **procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch**. Such control **procedures shall be established to** monitor the output and to **validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product**."

Further, demonstrating "adequacy of mixing" is only one of the applicable control procedure examples in **21 CFR 211.110(a)**.

The requirement stated is "Such **control procedures shall include**, but are not limited to, the following, where appropriate:

(1) Tablet or capsule weight variation;
(2) Disintegration time;
(3) **Adequacy of mixing to assure uniformity and homogeneity**;
(4) Dissolution time and rate;
(5) Clarity, completeness, or pH of solutions.

In addition, the commenter leaves out the critical requirement that their manufacturing process must be fully CGMP compliant.

Merck & Company's reviewed comments are as follows:

"Comment 1: Limitation of the scope of the guidance to validation and routine production, Lines 108-187

As noted above, we endorse the importance of developing a manufacturing process that guarantees consistent blend uniformity. This is a key step in our development and scale-up process, and we pay particular attention to the scale-up of the final blending step and design of the subsequent bulk powder transfer step in our manufacturing process trains. Based on our extensive development and scale-up experience, we have learned that the procedures one follows to characterize and mitigate blending and segregation issues are specific to the formulation and process equipment being used, and a "one size fits all" approach to blending and bulk transfer development is not flexible enough to allow a science-based

approach. For this reason, we feel that the development path described in Section IV Parts A-C is too prescriptive."

Since the document they are commenting on is guidance, that, unlike the CGMP regulations, in no way restricts the approaches that a manufacturer may choose to use to manufacture their drug products, this reviewer sees no compelling reasons for Merck to be concerned with the "prescription," if any, that is described in Section IV Parts A-C.

That having been said, this reviewer understands and accepts the validity of Merck's feelings here.

"We recommend that this section be generalized by replacing lines 108-187 with the following:

'Development of a manufacturing process that guarantees delivery of a powder blend of consistent content uniformity to the tablet press, encapsulator, or filling line is a critical piece of product development. It is therefore incumbent on manufacturers to develop robust final blending and subsequent bulk powder transfer steps to assure adequacy of mix and to demonstrate their robustness in process validation. The exact development path required for design of such a robust process depends on the formulation and the design of the manufacturing process equipment, and it should be based on application of appropriate scientific and engineering principles. An example of one development approach is described in the PQRI Blend Uniformity Working Group's final report.'"

Though this reviewer fully agrees with the commenter's opening statements, "Development of a manufacturing process… … science and engineering principles," this reviewer is disappointed that Merck's comments failed to note that the most important issue is that the manufacturing processes Merck develops are required by law to be fully CGMP compliant.

However, *because the approach in the "PQRI Blend Uniformity Working Group's final report" does not comply with the applicable clear requirements of the CGMP regulations*, this reviewer does not support this PQRI final report, and, by law (**see** Berkovitz v. USA, a unanimous 1988 decision by the US Supreme Court), the Agency cannot legally publish any guidance that does not conform to the clear applicable requirement ***minimums*** set forth in the CGMP regulations or any other binding FDA regulations.

Since the draft follows the CGMP-non-conforming recommendations of the PQRI, hopefully, the Agency will soon formally withdraw this clearly violative Draft and replace it with one that fully conforms to the clear CGMP regulations that are applicable to the topic of said Revised Draft, be it assessing batch uniformity (the general requirement) or, *as the current draft discusses*, the limited topic of assessing the active uniformity aspect of the batch (with other guidance for the other critical variable factors that must be assessed before one can assert the batch is uniform at the end of any significant manufacturing phase).

"Comment 2: Inflexibility of blender validation sampling requirements, Lines 194-215

While we agree that sampling of blends with a sampling thief is often the most practical way of characterizing blend uniformity in batch blending during a validation study, the sampling requirements in Section V of the guidance are too rigid, don't generally conform with good science practice, and may be impractical for certain blender designs. For example, the recommendation to take at least three replicate samples from each location is inconsistent with good sampling practice of not disturbing a static powder bed by repeated sampling. Also, the recommendation of sampling convective mixers in twenty locations is arbitrary and does not consider differences in blender design (i.e., ribbon blenders vs. high-shear mixers). Therefore, we suggest that the blender sampling requirements for process validation, lines 194-215, be replaced by the language describing blender sampling in process development, lines 123-137, which requires the manufacturer to design and evaluate appropriate blender sampling plans based on applications of good science and statistical principles."

While this reviewer does not disagree with most of the commenter's remarks, he does think that the language in Lines 194 – 215 should be modified rather than replaced as the commenter suggests.

To that end, this reviewer offers the following alternate wording for Lines 194 – 215:

"We recommend that during the manufacture of ***all*** *initial process conformance* ~~exhibit and process validation~~ batches, you assess the uniformity of the powder blend, the in-process dosage units, and the finished product ~~independently~~. We recommend you use the ~~following~~ steps in Section IV of this guidance to identify sampling locations and acceptance criteria prior to the manufacture of ~~the exhibit and/or validation~~ *any additional process conformance* batches beyond any near-production-scale initial technology transfer/demonstration process conformance batch produced to confirm the validity of your specifications, acceptance criteria, and inspection plans."

Because, as per **21 CFR 211.110(a)**, *all batches validate the process, all batches* are "validation batches."

Since it is clear that this section of the draft guidance is intended to address only the initial *process* validation batches that the Agency has *recently* (12 March 2004) formally labeled as initial "process conformance batches," this reviewer has modified the text accordingly.

"Comment 3: Inflexibility of stratified sampling locations for routine batches, Lines 313-315.

While we agree that stratified sampling of dosage units in routine batches is the best method for characterizing blend and content uniformity, we feel that the specification of "at least 10" sampling locations may be impractical and unnecessary to assess the uniformity of the blend in some cases, for example for small batch sizes. Also, the guidance provides no flexibility in either the number of or location of sampling points that would be necessary to accommodate interruptions in processing. We have conducted statistical simulations, similar to those done by the PQRI Blend Uniformity Working Group, to assess the sensitivity of the blend uniformity acceptance criteria in the Guidance to the number of sampling locations. This analysis, summarized in the Attachment, shows that the percentage of batches that fail the Standard Criteria Method (SCM) and Marginal Criteria Method (MCM) is insensitive to the number of sampling locations as long as (1) the total number of tablets assayed conforms with the Stage 1 and Stage 2 requirements specified in the Guidance and (2) tablets are sampled from at least five locations. For this reason, we believe that the recommendation of sampling from "at least 10 locations" is overly restrictive. We recommend changing lines 313-314 to read, 'You should identify at least 10 locations during capsule filling or tablet compression to represent the entire routine manufacturing batch. For very small batch sizes, it may not be practical to collect tablets from 10 locations; in this case, the batch should be sampled from no fewer than five locations. In the event that a sampling location is missed due to a filling or compressing interruption, a batch can also be sampled in fewer than 10 locations, but no fewer than 5 locations. In all cases, a sufficient number of tablets should be collected from each location to meet the testing requirements described in Section A below. Any deviations from this approach should be evaluated and justified using sound scientific and engineering principles.'"

First, as the commenter's remark clearly demonstrates, "While we agree that stratified sampling of dosage units in routine batches is the best method for characterizing blend and content uniformity," the commenter's statement knowingly ignores the following clear CGMP requirements:

1. All sample sets must be a *representative sample* of the batch (**21 CFR 211.160(b)(2)**) and not the non-representative samples that the Draft's "stratified sampling" plan generates.
2. *During the manufacture of each batch*, the in-process material produced by each significant phase (pre-blend, blended granulation, coated material, intermediate blend, final blend, formed dosage units, etc.) must "be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit" (**21 CFR 211.110(c)**) and not only does this draft not address all significant production phases, but it also does not address the required testing for other than "strength" nor the clear requirement that the "quality control unit" must approve or reject each material.
3. The reality that, *based upon the commenter's admission of the probability of some segregation during bulk transfer*, the weight-corrected active content in the dosage units is, at best, a *biased estimate* of the true blend active uniformity and no valid indicator *per se* of the uniformity of any other critical variable factor in the blend or the dosage units or its appropriate surrogate.
4. The reality that, *based on the recognized consensus standards (ISO 3951 and ANSI Z1.9) for discrete materials produced from less than rigorously defined components (the "process variability unknown—standard deviation" procedure or the "process variability unknown—range" procedure")*, the sample numbers specified in the Draft are insufficient for what is required.

Thus, the published draft recommends accepting or rejecting the untested batch based on the testing of an insufficient number of units.

5. The reality that the *specifications* established are not *scientifically sound* for the samples tested, are inadequate and/or inappropriate for the purposes required, and do not include the required derivative *batch-acceptance criteria*.
6. The "conclusions" reached by the PQRI Blend Uniformity Working Group in their final report are based on, *as the commenter points out*, biased and otherwise deficient blend inspection procedures.

While some of what the commenter's state in the text that follows the commenter's initial remark ("we feel that the specification of 'at least 10' sampling locations may be impractical and unnecessary to assess the uniformity of the blend in some cases, for example for small batch sizes. Also, the guidance provides no flexibility in either the number of or location of sampling points that would be necessary to accommodate interruptions in processing. We have conducted statistical simulations, similar to those done by the PQRI Blend Uniformity Working Group, to assess the sensitivity of the blend uniformity acceptance criteria in the Guidance to the number of sampling locations. This analysis, summarized in the Attachment, shows that the percentage of batches that fail the Standard Criteria Method (SCM) and Marginal Criteria Method (MCM) is insensitive to the number of sampling locations as long as (1) the total number of tablets assayed conforms with the Stage 1 and Stage 2 requirements specified in the Guidance and (2) tablets are sampled from at least five locations. For this reason, we believe that the recommendation of sampling from "at least 10 locations" is overly restrictive.") may have validity, the "scientific" simulations the commenter reports are:

- Based on the presumed validity of the mostly erroneous premises contained in the PQRI report upon which the draft guidance is based,
- Presume an unsubstantiated "normal" distribution for the active content results, and
- Fail (in the attachment) to provide complete data to permit any scientifically sound evaluation of the incomplete "findings" reported.

Rather than addressing the overly prescriptive language in the manner suggested by this commenter, this reviewer recommends deleting section VI. D and modifying the beginning portions of Section VII as follows:

"~~**D. Sample Locations for Routine Manufacturing**~~

~~We recommend that you prepare a summary of the data analysis from the powder mix assessment and stratified sample testing. From the data analysis, you should establish the stratified sample locations for routine manufacturing, taking into account significant process events and their effect on in-process dosage unit and finished dosage unit quality attributes. You should identify at least 10 sampling locations (or more) during capsule filling or tablet compression to represent the entire routine manufacturing batch.~~"

Lines 419-525 should be deleted from the draft guidance for all of the reasons cited previously concerning the need for batch uniformity to be assessed for *all* of the *critical* variable factors, not just active content, against the appropriate *scientifically sound* specifications.

21 CFR 211.110(a) clearly requires the monitoring of **all** variable factors that may be responsible for causing "variability in the characteristics of in-process material and the drug product."

Therefore, any general guidance on in-process uniformity must address all of the critical variable factors in a given formulation.

Because the guidance provided does not address *general uniformity* and the "stratified" sampling proposed does not ensure that *batch-representative samples* of either the final blend or, *as the term "stratified sampling" is defined*, the in-process dosage units are taken and tested, this reviewer cannot support the commenter's suggestions nor, for that matter, the original text.

Upon reflection, this reviewer clearly understands that the Agency should refrain from issuing any prescriptive language in this guidance because the nature, level and required degree of uniformity required to assure the requisite level of uniformity in the in-process materials and the drug product *varies from drug product to drug product*.

Based on the preceding realities, this reviewer recommends replacing **Lines 419-525** with the with the following text:

"**VII. ROUTINE MANUFACTURING BATCH TESTING ~~METHODS~~ PROCEDURES**

You should use the outcomes observed in Section VI and the hierarchical sample testing procedures and switching rules (derived from those in the appropriate consensus standards for batch-representative dosage units and those developed using the appropriate valid statistical procedures found in text treating the general uniformity of non-discrete materials for the batch representative samples from blends) to control the inspection procedures used for each batch.

You should use the *scientifically sound* and *appropriate specifications, sample and batch acceptance criteria,* and *other process controls* that comply with all the applicable strictures of **21 CFR 211.110** and **21 CFR 211.165** to control, monitor and validate each *phase* (or stage) in the manufacture of each batch.

In addition, at each 'periodic review,' *or when there are any material improvements in the controls or significant improvements in the uniformity outcomes*, the manufacturers should review the entire historical data file and act when, and as, the data therein indicate. Based on that review, the firm should either confirm the validity of the existing manufacturing criteria (specifications, sample and batch acceptance criteria, and other process controls) or use the information obtained to justify any change that modifies the firm's CGMP-compliant approved inspection plans including any revision in the number of batch-representative samples to be evaluated for a given variable factor.

In all cases, the manufacturers who wish to reduce their testing can develop, prove, and apply their proven *scientifically sound* and *appropriate* hierarchical (staged) evaluation plans (with acceptance criteria that are established as being both *scientifically sound* and *appropriate*) to each phase of manufacturing.

In addition, for partially correlated variable factors (such as active content and active availability, or active content and active impurity/degradant level) which are evaluated by testing, the manufacturer should used their justified 'REDUCED'

inspection plans for each of the correlated variable factors that, as the manufacturer established in Section VI, provide a *scientifically sound* and *appropriate* confidence level and risk that is not significantly greater than the risk for the 'NORMAL' inspection plans as the starting point for the assessment of the uniformity of the output of each phase (or stage) of manufacturing."

"**Attachment: Simulation of Blend Uniformity Test Results**

The results reported here are based on a Monte Carlo simulation using normal distributions for location averages and within location results. For each set of conditions, 10,000 lots were simulated. The number of lots passing each set of criteria were counted and divided by 10,000 to calculate the pass percentages. The lots were process in order to determine the pass rates we might expect in actual operation with SCM-to-MCM switching rules in place.

We varied the overall RSD for tablets from 2-6% and examined different proportions of within- and between-location variation:

80% Within/20% Between (a realistic split of variation based on past experience)
20% Within/80% Between (a large amount of between location variation) lots

The results summarized below compare the pass percentages of stratified testing of ten and five locations, In the 5-location simulation, we assumed two tablets were taken from each location for Stage 1 testing and six tablets were taken from each location for Stage 2 and MCM testing.

Results:

Table 1: Overall Pass Rates for 80/20 and 20/80 Location Variation Splits.

	80/20		20/80	
RSD	10 Locations	5 Locations	10 Locations	5 Locations
	100	100	100	100
	100	100	100	100
	100	100	100	100
	100	100	100	100
	100	100	99	98
	100	100	99	97
	99	99	97	94
	98	98	94	92
	94	94	89	88
	79	81	78	79
	56	59	62	69

These results show that the pass percentage is insensitive to the number of stratified sampling locations."

While this reviewer finds the commenter's statistical simulation interesting, he notes that the conclusion reported is false because no simulation can show anything; it can only estimate what the real situation is.

Moreover, the commenter's results tabulation and conclusion statement are knowingly deceptive because, among other deficiencies, the tabulation omits the RSD levels and the conclusion statement fails to indicate the *level of confidence* associated with the finding reported.

That confidence level depends upon many factors, but it is fairly low (less than 20 %) here, because the number of values simulated for each batch is in the range of 10 to 30 units from batches that consist of hundreds of thousands or millions of units.

Finally, the basis assumptions, *normal distribution* of values and the validity of the specifications and controls established in the Draft are unsupported, in the first instance, and invalid in the others.

On the whole, the commenter's statistical exercise seems to be but a pseudo-scientific exercise (statistical junk science) designed to support the commenters' position with little or no regard for what the real situation – much, *as to their credit this commenter recognizes in the firm's remarks*, like the PQRI Blend Working Groups' repeated and ongoing "apples and oranges" comparisons of "a batch-non-representative set of biased blend result values derived from samples obtained by, at best, questionable sampling practices" to "a subsequent testing of a few non-correlated batch-non-representative dosage units for a single variable factor, active level."

Hopefully, this reviewer's remarks have adequately addressed the formal comments submitted by this commenter.

Reviewer's Summary

Overall, this reviewer found that most of the commenters whose comments he reviewed were not particularly interested in or concerned with:

- ❖ CGMP compliance
- ❖ Sound science
- ❖ Appropriate procedures and practices
- ❖ Knowing the true uniformity of each batch of their in-process materials and drug products.

Rather their primary interests were, *with few exceptions*, in:

- – Doing even less than the Draft suggests
- – Pointing out apparent deficiencies in the Draft without providing either a *scientifically sound* or *CGMP-compliant* alternative
- – Adding "legitimacy" to this inherently flawed and non-CGMP-conforming draft guidance

Hopefully*, based on the CGMP-conforming and scientifically sound inputs provided by this reviewer and others*, the Agency will:

- ❖ Formally withdraw the current flawed "Draft Guidance" that plainly does not conform to the clear applicable CGMP requirement ***minimums*** for in-process materials and in-process (unreleased) drug products.
- ❖ Issue a clearly CGMP-conforming "Revised Draft Guidance" limited to "Assessing Active Uniformity" that is based on the scientifically sound and CGMP-conforming suggestions received for the industry to review and comment on, and, based on the cogent comments received thereto, issue a CGMP-conforming, sound-science-based "Final Guidance to Industry" on the narrow subject of "Assessing the Drug Product Batch Uniformity of Final Blends and Formed Dosage Units for the Active or Actives Therein," or
- ❖ Issue a CGMP-conforming, sound-science based "Draft Guidance to Industry" on the broader subject of "Assessing the Drug Product Batch Uniformity of In-process Non-Discrete Materials (e.g., Pre-blends, Granulations, Coated Powders, Intermediate Blends, and Final Blends) and Dosage Units (In-process and Finished) for All Established Critical Variable Factors."

If the Agency chooses the first draft replacement action, then the applicable CGMP-conforming and/or scientifically sound comments provided by this reviewer and others should make it easy for the Agency to quickly issue a CGMP-conforming "Revised Draft" for review and comment.

Otherwise, the Agency will need to gather more CGMP-conforming information before it can issue a suitable "Revised Draft."

Finally, given the non-conformity to CGMP and lack of sound science evident in this published Draft and in the comments made to this docket by the Industry, it would seem that the responses to this Agency Draft have revealed that many firms seem not to be complying with the clear applicable ***minimums*** set forth in the CGMP regulations for finished pharmaceuticals (**21 CFR Part 211**).